Principles of feeding the preterm infant

J. Hulst (NL)
Principles of feeding the preterm infant

Jessie Hulst, MD, PhD
Pediatric gastroenterologist
Erasmus MC-Sophia Children’s Hospital
Rotterdam, the Netherlands
Sept 7th 2014
Learning objectives

- Understanding the differences in pre- and postnatal growth factors
- The importance and impact of early aggressive nutritional support
- Timing of nutritional support concerning start of parenteral and enteral nutrition
- Supplementation of vitamins and micronutrients
- Treatment of parenteral nutrition-associated liver disease
Challenge for the neonatologist

- **Past 25 years:** dramatic improvement in neonatal medicine
  - regular survival of pretermly born infants from 24 weeks gestational age with birthweights of 500-600 g
  - very small, immature infants relatively common in NICU’s nowadays
  - survival creates a significant dilemma for neonatologists
  - how do they achieve growth of 2 to 3 kg of healthy body mass in these infants over a 12- to 16-week postnatal period?

  William Hay 2006
Goal of feeding VLBW infants

Achieve growth similar to fetal growth rates with similar body composition coupled with satisfactory functional development (Corpeleijn et al 2010)

AAP recommendation:
Postnatal growth rate of preterm infants duplicates fetal growth, in quantity and in quality, so that body size and body composition of preterm infants at term-corrected age are equal to those of the term-born infants
The importance of growth

- Low weight
- Diminished growth organs
- Altered structure and function
Brain development

25 wk

Term age
Do we achieve this goal?

The incidence of extra-uterine growth retardation varies between 43%-97% in various centres

Van Haesebrouck P et al Pediatrics 2004
Weight for age-SDS and follow-up preterms

Legend:

A: admission
B: discharge
C: 6 w after discharge
D: 6 m after discharge

*: p < 0.05 compared to A
†: p < 0.05 compared to B
‡: p < 0.05 compared to C

Hulst J et al Clinical Nutrition 2004
Why do we not achieve the goal?

Most important contributor to EUGR is underfeeding

- Fear of intolerance of fluid and nutrients during conditions such as sepsis, respiratory failure, asphyxia
- Fear of metabolic derangement due to suboptimal composition of the solutions
- Concept that anabolism can not be achieved until 5-7 days after birth
- Fluid intolerance during the first days
Factors associated with EUGR

- male gender
- need for assisted ventilation on day 1 of life
- a history of necrotizing enterocolitis
- oxygen dependency at 28 days of age
- need for steroid use during the hospital stay

De Curtis M and Rigo J 2004
What are the consequences of postnatal growth restriction in a VLBW infant?

Slow growth during neonatal period → Poor neurodevelopmental outcome

- Franz AR et al. Pediatrics 2009
- Weisglas-Kuperus N et al. Arch Dis Child 2009
In hospital growth velocity and neurodevelopment

(n=600; 501-1000g) Ehrenkranz, R.A. Pediatrics 2006;117:1253-61
Postnatal growth rather than SGA/AGA at birth determines later neurodevelopmental outcome

$\text{Bayley developmental scores}$

$Z$-score

- Good outcome
- Poor outcome
- Moderate outcome

Postnatal growth rather than SGA/AGA at birth determines later neurodevelopmental outcome

Current feeding strategy

Early aggressive parenteral nutrition, containing appropriate amounts in quantity and quality of carbohydrates, proteins and lipids
Growth: targets

Ideal growth = intra-uterine growth + catch up growth

Weight increase = ~18-20gr/kg/d\(^1\)
Height increase = ~ 1 cm/wk\(^2\)
Head circumference = ~ 1 cm/wk\(^2\)

\(^1\) Ehrenkranz et al Pediatrics 2006
\(^2\) Ehrenkranz et al Pediatrics 1999
## Energy intake vs body weight

<table>
<thead>
<tr>
<th>Body weight (g)</th>
<th>500-700</th>
<th>700-900</th>
<th>900-1200</th>
<th>1200-1500</th>
<th>1500-1800</th>
<th>1800-2200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal weight gain&lt;sup&gt;1&lt;/sup&gt;</td>
<td>21</td>
<td>20</td>
<td>19</td>
<td>18</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Required energy intake parenteral&lt;sup&gt;1&lt;/sup&gt;</td>
<td>89</td>
<td>109</td>
<td>101</td>
<td>108</td>
<td>109</td>
<td>111</td>
</tr>
<tr>
<td>Required energy intake enteral&lt;sup&gt;2&lt;/sup&gt;</td>
<td>105</td>
<td>118</td>
<td>119</td>
<td>127</td>
<td>128</td>
<td>131</td>
</tr>
</tbody>
</table>

<sup>1</sup> needed to obtain weight gain (g/kg/day);
<sup>2</sup> needed to obtain weight gain (kcal/kg/day)

Ziegler et al Ann Nutr Metabol 2011
Can we start early nutrition irrespective of the severity of illness?


**Early Nutrition Mediates the Influence of Severity of Illness on Extremely Low Birth Weight Infants**


1366 participants randomized according to severity of illness during the first week of life

Result: The influence of critical illness on the risk of adverse outcomes was mediated by the total daily energy intake during the first week of life
What should we do in the first week of life?

Agenda summary:

- TPN can be initiated safely from the first day of life
- Consider amount of fluids up to 200 ml/kg
- Carbohydrate intake up to 12 mg/kg min and treatment with insulin in case of hyperglycaemia
- AA supply up to 3,5 g/kg/day from the first day of life is well tolerated and achieve earlier weight gain.
- Lipids can be initiated safely from the first or second day of life
Rationale for early initiation of TPN

First-Week Protein and Energy Intakes Are Associated With 18-Month Developmental Outcomes in Extremely Low Birth Weight Infants

Retrospective study of 124 ELBW infants at 18 months CA
Fluid: what is known?

- Fluid tolerance is limited in the first day of life due to renal readjustment but large variability among VLBW infants → need to monitor urinary output

- Restricted fluid supply within the first days results in decreased incidence of patent ductus arteriosus, BPD and NEC (Bell et al. Cochrane review 2010)

- Fluid intake is increased in the first week of life and 135 ml/kg/day is the minimum and 200 ml/kg/day the upper limit
Carbohydrates

- Carbohydrates are a major source of energy
- Glucose is the primary source of energy for the brain and the only carbohydrate in PN
- In utero transfer of glucose across the placenta averages 8mg/kg/min
- In VLBW infants endogenous glucose is inadequate to provide the demands, therefore glucose should be administered
- Insulin response to hyperglycemia is limited in VLBW infants

Chacko SK et al. Arch Dis Child Fetal Neonatal 2010
Carbohydrates: current guidelines

- Start glucose infusion at birth: 6 mg/kg/min.
- Increase rate daily with 1-2 mg/kg/day or more frequently
- If hypoglycemia (<50mg/dl or 2.7 mmol/l) occurs to a max of 12 mg/kg/min
- If blood glucose exceeds 145 mg/dl (8.0 mmol/l) consider insulin infusion at a rate of 0.01-0.04IU/kg/h and increase up to 0.2 IU/kg/h to keep glucose level below 145 mg/dl
Protein

- Amino acids (AA) are pivotal in early life as precursors for proteins (and thus growth) and neurotransmitters, as transport molecules and in cell signalling
- Aa are classified as essential or non-essential
- Of the 20 amino acids 9 are essential
- Due to immaturity of different enzyme systems, premature infants are not able to synthesize an additional 4 amino acids; arginine, glycine, proline and tyrosine (conditionally essential amino acids).

<table>
<thead>
<tr>
<th>Table 4. Subdivision of amino acids into non-essential, essential, and so-called ‘conditionally’ essential amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-essential</strong></td>
</tr>
<tr>
<td>alanine</td>
</tr>
<tr>
<td>serine</td>
</tr>
<tr>
<td>asparagine</td>
</tr>
<tr>
<td>aspartate</td>
</tr>
<tr>
<td>glutamate</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
### Table 3. Protein requirements and recommended intakes

<table>
<thead>
<tr>
<th></th>
<th>Weight &lt;1,200 g</th>
<th>Weight &gt;1,200 g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/kg/day</td>
<td>g/100 kcal</td>
</tr>
<tr>
<td>Ziegler (table 1)</td>
<td>4.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Kashyap and Heird [34]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rigo [35]</td>
<td>3.8–4.2</td>
<td>3.3</td>
</tr>
<tr>
<td>LSRO [37]</td>
<td>3.4–4.3</td>
<td>2.5–3.6</td>
</tr>
<tr>
<td>ESPGHAN 2010 [38]</td>
<td>4.0–4.5</td>
<td>3.6–4.1</td>
</tr>
</tbody>
</table>

LSRO = Life Sciences Research Office; ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology and Nutrition.
Protein: Current guidelines

- Start AA supply on the first postnatal day: 2.4 g/kg/day
- Increase to 4.0 - 4.5 g/kg/day for infants up to 1000 g and 3.5 – 4.0 g for infants from 1000 to 1800 g
- The amino acid intake can be reduced towards discharge if the infant’s growth pattern allows for this

- Tolerance of amino acid infusions is commonly measured by plasma urea concentrations and ammonia concentrations
Lipids

Dietary lipids provide:
1. Calorie-dense nutrients (9 kcal/g) with low CO2 production
2. Essential polyunsaturated fatty acids (PUFA’s)
3. Lipid soluble vitamins

- Saturated fatty acids serve primarily as energy source
- Polyunsaturated fatty acids play a role as components of structural lipids
# Lipids: major classes and function

<table>
<thead>
<tr>
<th>Lipid class</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycerides</strong></td>
<td>Fatty acid storage, metabolic intermediates</td>
</tr>
<tr>
<td>-esterification of glycerol and fatty acids</td>
<td></td>
</tr>
<tr>
<td><strong>Phospholipids</strong></td>
<td>Membrane structure, lung surfactant</td>
</tr>
<tr>
<td>-phosphorus containing lipid compounds</td>
<td></td>
</tr>
<tr>
<td><strong>Sterols</strong></td>
<td>Membrane and lipoprotein structure, precursors of steroid hormones, degradation products are bile salts important in fat digestion and absorption Storage and transport</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
</tr>
<tr>
<td>Cholesteryl ester</td>
<td></td>
</tr>
<tr>
<td><strong>Fatty acids</strong></td>
<td>Major energy source, components of most lipids, precursors of prostaglandins</td>
</tr>
</tbody>
</table>
# Nomenclature of fatty acids

<table>
<thead>
<tr>
<th>Length of carbon chain</th>
<th>Short ≤ 6 carbon atoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medium 8-10 carbon atoms</td>
</tr>
<tr>
<td></td>
<td>Long ≥ 12 carbon atoms</td>
</tr>
<tr>
<td></td>
<td>Very long ≥ 22 carbon atoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amount of double bounds</th>
<th>No double bounds: saturated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 double bound: mono-unsaturated</td>
</tr>
<tr>
<td></td>
<td>≥2 double polyunsaturated</td>
</tr>
<tr>
<td></td>
<td>n-3 family first double bound from</td>
</tr>
<tr>
<td></td>
<td>terminal methyl</td>
</tr>
</tbody>
</table>
PUFA’s = poly unsaturated fatty acids

α - Linolenic acid (C18:3 n-3) → Docosahexaenoic acid DHA(C22:6 n-3)

Linoleic Acid (18:2 n-6) → Arachidonic acid AA (C20:4 n-6)
Essential fatty acids

Polyunsaturated fatty acids of the n-6 series and n-3 series (linoleic acid (LA) and (α-linolenic acid (ALA)) cannot be synthesized de novo by higher organisms and are essential nutrients.

In VLBW infants there is a limited capacity to synthesize arachidonic acid (AA) and docosahexaenoic acid (DHA) from LA and ALA and these fatty acids are also considered essential.

Clinical trials in preterm infants fed formulae containing both AA and DHA have shown beneficial effects on the developing visual system and measures of cognitive development during the first year of life.
Current recommendations lipids

- Start intravenous lipids not later than 3rd day of life
- Maximum dose of parenteral lipid administration is 3-4 g/kg/day
- Can be reached within 3 days from starting
- To prevent essential fatty acid deficiency, 0.25 g/kg.d linoleic acid should be included

- Recommended intake for DHA 12 to 30 mg/kg/day and for AA 18 to 42 mg/kg/day (ratio DHA-AA 1:2)

- The tolerance of lipids can be checked by determining plasma triglyceride and cholesterol levels
Monitoring of lipid supply in TPN

<table>
<thead>
<tr>
<th>Serum triglycerides mmol/l</th>
<th>Intervention</th>
<th>Check serum values</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>continue according to normal protocol</td>
<td>according to local protocol</td>
</tr>
<tr>
<td>3–4</td>
<td>continue at 50% of dosage</td>
<td>next day</td>
</tr>
<tr>
<td>4–5</td>
<td>continue at 25% of dosage</td>
<td>next day</td>
</tr>
<tr>
<td>&gt;5</td>
<td>stop</td>
<td>next day</td>
</tr>
</tbody>
</table>

Parenteral nutrition associated liver disease (PNALD)

Spectrum from mild cholestasis to end stage liver disease

Risk factors:

- Reduced bile acid pool size
- Immature enterohepatic circulation

High levels of phytosterols and n-6 PUFAs in soybean oil
Parenteral lipids: newer generations?

First generation

Intralipid 20%, soybean oil, very rich in ω-6 PUFA

Newer generations (SMOF-lipid, Omegaven)

MCT/LCT mixtures and olive oil containing emulsions

Soybean-LCT, MCT, olive oil and fish oil, supplemented with Vitamin E (designed to increase the amount of ω-fatty acids, thereby reducing the ratio ω-6: ω-3 fatty acids)
New lipid emulsions?

Parenteral lipid administration to very-low-birth-weight infants—early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis\textsuperscript{1–3}  


*Hester Vlaardingerbroek, Margriet AB Veldhorst, Sandra Spronk, Chris HP van den Akker, and Johannes B van Goudoever*

- Initiation of lipids < first 2 d of life in VLBW infants: safe and well tolerated
- Beneficial effects on growth could not be shown for this treatment nor for the type of lipid emulsion
- Emulsions that are not purely soybean oil–based might be associated with a lower incidence of sepsis
- Large-scale randomized controlled trials in preterm infants are warranted to determine whether early initiation of lipids and lipid emulsions that are not purely soybean oil–based results in improved long-term outcomes
When to start enteral feeding in VLBW infants?

What is known?

- At birth the GI tract of the VLBW infant:
  - Is immature both morphologically and functionally
  - Has also immature motility
  - Lacks microbiota or harbours abnormal microbiota
    ➞ all predisposing for NEC

- Late onset of enteral feeding does not prevent from NEC
- Immature GI tract is capable of rapid maturation in response to stimulation by feeding
- The sole objective of early feeding (often referred as trophic feeding) is to hasten maturation
When to start enteral feeding in VLBW infants?

Current practice

- Start trophic feeding as soon as possible (D1-D2)
- Preference for own mother’s milk
- Bolus feeding is better tolerated than continuous feeding
- There is no general consensus about the safe use of probiotics
When to start enteral feeding in VLBW infants?  
**Current practice? (2)**

Cochrane review 2014 Probiotics:

- Enteral supplementation of probiotics prevents severe NEC and all cause mortality in preterm infants
- Available evidence strongly supports a change in practice
- Head to head comparative studies are required to assess the most effective preparations, timing, and length of therapy to be utilized.
Breast milk: recommendation

- Human milk provides antibodies, enzymes, probiotics, hormones and growth factors
- Human milk provides optimal PUFA content and optimal Ca en Fe absorption
- Human milk has low protein and energy content and therefore add fortifier:
  - To meet the infant's nutritional requirements
  - It contains extra protein, energy, vitamins and minerals
  - Fortifiers contain approximately 0.8 g of protein per 100 ml of milk
  - Fortification can be started when 100 ml/kg of enteral feeding is tolerated
- Catch-up growth and obesity early in life is associated with metabolic syndrome in later life.
- Current guidelines recommend special post-discharge feeding for preterm infants until an SD score of -1 is reached and for no longer than 6 months after term.
Feeding strategy

- **Start glucose infusion at birth**: 6 mg/kg/min
- **Euglycaemia defined as** <145 mg/dl (8.0 mmol/L). Consider insulin treatment >8 mmol/L
- **Increase daily or more frequently, with** 1-2 mg/kg/min
- **Start amino acid infusion at birth**: 2.4 g/kg/day
- **Within 2-4 days increase to** 4.0- g/kg/day
- **Start lipid infusion at day 1 (latest day 3)**: 1 g/kg/day and increase to 3-4 g/kg/day in 3 days
- **Target 90-110 kcal/kg/day for optimal growth**

| Birth to day 1 | Few day after birth | Several days to 1 week | Erasmus MC |
Conclusions

- Nutritional support of the VLBW infant should be started as early as possible, not only for growth but also for optimal neurocognitive development.
- The in-hospital postnatal growth rate of preterm infants should approach fetal growth.
- Nutrition may need to include TPN in the first few days after birth as intestinal function is immature.
- The PN should supply the full requirements and contain a generous provision of AA.
- Start with minimal enteral feeding on the day of birth in infants who are not able to receive normal enteral feeding.
- There is a strong preference for milk from the child's own mother.
Questions?

ACKNOWLEDGEMENTS
Erasmus MC, Sophia Children’s hospital
- Koen Joosten, pediatric intensivist
- Marijn Vermeulen, neonatologist
- Jorine Roelants, research physician

VUMC Amsterdam
- Harrie Lafeber, neonatologist