What is the optimal nutrition for the (preterm) newborn?
Breastfeeding: Meta-analysis on long term effects

- Systolic RR $\downarrow$ 1.5 mmHg
- Diastolic RR $\downarrow$ 0.5 mmHg
- Total cholesterol $\downarrow$ 7 mg/dL
- LDL cholesterol $\downarrow$ 7.7 mg/dL
- Diabetes type 1 $\downarrow$ 19-27 %
- Diabetes type 2 $\downarrow$ 39 %
- Overweight $\downarrow$ 7-24 %

Addressing uncertainties: alternatives to classic randomization trials (The Probit Trial, Kramer et al)

1. The PROmotion of Breastfeeding Intervention Trial, a cluster randomization trial based on the WHO UN Children’s Fund Baby Friendly Hospital initiative

2. Enrolled 17,046 healthy breastfeeding mother-infant pairs from 31 Belarusian maternity hospitals and polyclinics

3. The experimental intervention led to a large increase in exclusive breastfeeding at 3 months (43.3% vs 6.4%) and a significant higher prevalence of any breastfeeding at all ages up to and including 12 months.

4. High follow-up rate
**Lessons from Probit: benefits of breastfeeding**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal tract infection</td>
<td>1 y</td>
<td>Reduced</td>
</tr>
<tr>
<td>Atopic eczema</td>
<td>1 y</td>
<td>Reduced</td>
</tr>
<tr>
<td>Respiratory Infection</td>
<td>1 y</td>
<td>No benefit</td>
</tr>
<tr>
<td>Asthma and allergy</td>
<td>6.5 y</td>
<td>No benefit</td>
</tr>
<tr>
<td>Child and maternal behaviour</td>
<td>6.5 y</td>
<td>No benefit</td>
</tr>
<tr>
<td>Height</td>
<td>6.5 y</td>
<td>No benefit</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>6.5 y</td>
<td>No benefit</td>
</tr>
<tr>
<td>Dental caries</td>
<td>6.5 y</td>
<td>No benefit</td>
</tr>
<tr>
<td>Cognitive development</td>
<td>6.5 y</td>
<td>Improved</td>
</tr>
<tr>
<td>Overweight and obesity</td>
<td>11.5 y</td>
<td>No benefit</td>
</tr>
<tr>
<td>Problematic eating attitude</td>
<td>11.5 y</td>
<td>Reduced</td>
</tr>
<tr>
<td>Breastfeeding of subsequent child</td>
<td></td>
<td>Improved</td>
</tr>
</tbody>
</table>

**Breast-feeding and cognitive development: a meta-analysis**

*James W. Anderson, Bryan M. Johnstone, and Daniel Y. Remley*  
*Am J Clin Nutr 1999;70:525–35*

- Breastfeeding is associated with a cognitive benefit (3.16 points; 95% CI 2.35 – 3.98)
- Benefit is greater in low birth weight infants (5.18 points, 95% CI 3.59-6.77) than in normal-weight-infants (2.66 points, 95% CI 2.15-3.17)
Breast-feeding and cognitive development: a meta-analysis\textsuperscript{1-3}

James W Anderson, Bryan M Johnstone, and Daniel T Remley

\textit{Am J Clin Nutr} 1999;70:525–35

Cognitive benefits association increases with duration of breastfeeding

Comparing countries
Prematurity: how large is the problem?

- 7% of all European neonates (Poland 6.8%) are born premature (500,000/yr)
- 12% of all US neonates are born premature (480,000/yr)
- 8% of all Chinese neonates are born premature (1,500,000/yr)
- 6% of all Japanese neonates are born premature (600,000/yr)

- Mortality: 11% < 1500 grams

- At age 19 years:
  - 13% moderate to severe handicap
  - 53% mild handicap
  - 3x more frequently unemployed or not at school

1 Hille et al. Pediatrics 2007
Survival rates of very preterm infants are increasing

Survival by Gestational Age for Live-Born Infants

- Europe 1995
- Europe 2005-2007

- 23 wks
- 24 wks
- 25 wks
Goal:
To mimick intra-uterine growth and body composition
and to obtain a functional outcome comparable to infants born at term

(ESPGHAN CoN JPGN 2010; 50;85-91)

Human Growth is Special

The priority of human development is the brain.

From: M Crawford
Different principles for body growth and brain growth
At four years of age this animal weighs 1 ton but its brain weighs only 350g

Which mammal has a greater requirement for components to support its brain?
Mammalian brain growth spurt

- Myelination
- Synaptogenesis
- Apoptosis
- Neuronal migration

Increase in brain size

24w 90% volume 2y

25 wk term

24 wk premature, now 12 wks old

Term newborn

Govaert et al
Relationship of IQ and GA

Explanation for lower cognitive outcomes in children born at low gestational ages:

- Inflammation
- Infections
- Oxidative stress
- Infarction, hemorrhages
- Insults due to low oxygen supply
- Reduced availability of appropriate substrates

Adapted from Lagercrantz Acta Paed. 2008

Van den Berg et al 2005
Rook et al 2010
Impact of Nutrition
Lucas et al 1998
Van den Akker 2014
Early nutrition (first weeks-months) has a profound impact on later functional outcome

Quantity matters

Effects of Undernutrition at Different Ages Early in Life and Later Environmental Complexity on Parameters of the Cerebrum and Hippocampus in Rats

IQ of preterm infants fed a preterm formula or standard formula during the first month of life assessed at age 7-8 years


Caudate volume is influenced by early nutrition and related selectively to Verbal IQ in males, but not in females.

Isaacs Pediatr Res 2008 N=76 adolescents
Even the first few days seem to have an impact on later functional outcome.
First week protein and energy intake and neurodevelopmental outcome @18 months

- Retrospective study of 124 extremely low birth weight infants (<1 kg birth weight at 18 months corrected age)
- AA intake 1st week: 1.8 ± 0.4 g/(kg·d)
- Energy intake 1st week: 60 ± 8 kcal/(kg·d)

NIPI-1 study

control 1.2 g/(kg·d) amino acids 2.4 g/(kg·d)

intervention amino acids 2.4 g/(kg·d)

time after birth (h)

Van den Akker 2005-2008
Te Braake 2005-2008
Glutathion kinetics improve following amino acid supplementation

Glutathione Synthesis Rates in Early Postnatal Life

DENISE ROOK, FRANS W. J. TE BRAAAKE, HENK SCHERBEEK, MARIANGELA LONGINI, GIUSEPPE BUONOCORE, AND JOHANNES B. VAN OUDOWERE

Department of Pediatrics [D.R., F.W.J.B., H.S., J.B.G.], Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands; Department of Pediatrics [M.L., G.B.], Obstetrics and Reproductive Medicine, University of Siena, Policlinico “Le Scotte,” 53100 Siena, Italy


Long term safety and efficacy
Boys, but not girls, benefit from early amino acids on day 1 and 2

Alive without major handicaps

Quality of nutrition matters especially in preterm infants
Effects of own mothers milk

Infections: 47% vs 29%

Incidense Necrotiserende Enterocolitis 6x↓
- Lucas et al., Lancet 1990

Tolerance for enteral nutrition improved
- Schanler et al., Pediatrics 1999

Readmittance to hospital following discharge ↓
- Vohr et al., Pediatrics 2006

Blood pressure at 13-16 years

<table>
<thead>
<tr>
<th></th>
<th>Human milk</th>
<th>Preterm formula</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic</td>
<td>61.9</td>
<td>65.0</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean</td>
<td>81.9</td>
<td>86.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Singhal Lancet 2001
Effects lower blood pressure

<table>
<thead>
<tr>
<th>Diast. RR (mmHg)</th>
<th>0.6</th>
<th>1.2</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD risk reduction</td>
<td>3%</td>
<td>6%</td>
<td>11%</td>
<td>21%</td>
<td>38%</td>
</tr>
<tr>
<td>Stroke risk reduction</td>
<td>5%</td>
<td>10%</td>
<td>19%</td>
<td>34%</td>
<td>56%</td>
</tr>
</tbody>
</table>

HTA 2003; 7(31)

Nutrition (quality and quantity) influences blood pressure, insulin sensitivity, HDL/LDL ratio and cognitive function in ex-prematures

Rotteveel Horm Res Paediatr. 2011;75:252-7
Finken J Clin Endocrinol Metab. 2011;96:E1650-5
Growth (Nutrition) has a major impact on later outcome.
What are our results in preterm infants?
Ehrenkranz '99

NICHD Growth Observational Study

Mean growth curves of weight by postmenstrual age and week of gestation, superimposed on the British 1990 birth weight reference.

There is a need for good guidelines, but guidelines need to be implemented as well.
Guidelines

Enteral Nutrient Supply for Preterm Infants: Commentary From the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition

TABLE 1. Recommended intakes for macro- and micronutrients expressed per mg·kg⁻¹·day⁻¹ and per 100 kcal unless otherwise denoted

<table>
<thead>
<tr>
<th></th>
<th>Per kg⁻¹·day⁻¹</th>
<th>Per 100 kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid, mL</td>
<td>135–200</td>
<td></td>
</tr>
<tr>
<td>Energy, kcal</td>
<td>110–135</td>
<td></td>
</tr>
<tr>
<td>Protein, g &lt;1 kg body weight</td>
<td>4.0–4.5</td>
<td>3.6–4.1</td>
</tr>
<tr>
<td>Protein, g 1–1.8 kg body weight</td>
<td>3.5–4.0</td>
<td>3.2–3.6</td>
</tr>
<tr>
<td>Lipids, g (of which MCT &lt;40%)</td>
<td>4.8–6.6</td>
<td>4.4–6.0</td>
</tr>
</tbody>
</table>
CSPEN guideline for nutrition support in neonates

Working group of Pediatrics, Chinese Society of Parenteral and Enteral Nutrition
Working group of Neonatology, Chinese Society of Pediatrics
Working group of Neonatal Surgery, Chinese Society of Pediatric Surgery

Recommended intakes

1. **Energy**: Most of neonates will have an optimal growth when enteral feedings provide 105–130 kcal/kg/d. Increased energy intake in premature infants (110–135 kcal/kg/d) and extremely low birth weight infants (150 kcal/kg/d) will meet the needs of these neonates (C).

2. **Protein**: Protein intake of term infants is 2–3 g/kg/d with a protein/energy ratio of 1.8–2.7 g/100 kcal. Protein intake of premature infants is 3.5–4.5 g/kg/d (4.0–4.5 g/kg/d in infants weighting less than 1 kg at birth, 3.5–4.0 g/kg/d in infants weighting 1.0–1.8 kg at birth) with a protein/energy ratio of 3.2–4.1 g/100 kcal (C).
Compliance to existing guidelines:

- Initiation with amino acids on d0: 63%
- Initial dose > 1.5 g/kg/d: 38%

Parenteral amino acid requirements

- Starting with 2,5 g/kg/d results in beneficial effects demonstrated with biomarkers and
- is associated with improved long term outcomes in boys
- while appears to be safe in all
Parenteral nutrition requirements

New guidelines to be developed in 2015

• Early diet has a huge impact on later outcome

• Human milk offers long term benefits, and preterm infants are at risk for appropriate development.

• Even first week nutritional (amino acid) management in preterm infants is associated with impact on long term