Controversies in Nutrition of the Very Low Birthweight Infant

Josef Neu, M.D.
Neonatal Biochemistry, Nutritional and Gastrointestinal Development Laboratory
University of Florida
Dr. Neu has disclosed the following relevant financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

<table>
<thead>
<tr>
<th>Affiliation / Financial Interest</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant Microbial Therapeutics</td>
<td>Consultant</td>
</tr>
<tr>
<td>Medela</td>
<td>Scientific Advisory Board</td>
</tr>
</tbody>
</table>

I will not discuss any off-label use and/or investigational use in my presentation.
Agenda

- The Nutritional **Emergency** of Extremely Low Birthweight Preterm Birth.
- Neurodevelopmental Consequences of Early Undernutrition.
- Nutritional Strategies: Early Parenteral and Enteral Nutrition
- Can we feed these infants enterally?
AGA 27 week : How do we nourish this baby?
Parenteral Nutrition: Common Practice

• Amino acids started in first week of life and advanced slowly in increments.
• Lipid infusions started in first week of life and advanced incrementally.
• Amino acids and lipids frequently delayed or interrupted.
Excuses To Withhold ENTERAL “Feedings”

- Low APGAR scores.
- Umbilical catheters.
- Apnea and Bradycardia.
- Mechanical ventilation.
- CPAP.
- Vasoactive drugs.
- TPN is available.
Calorie intake and cumulative deficit over the first 10 days: 50 British NICUs

Grover A et al. JPEN J Parenter Enteral Nutr 2008;32:140-144
Protein intake and cumulative deficit over the first 10 days: 50 British NICUs
Energy Stores in the Fetus and Newborn

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Wt (g)</th>
<th>Water (%)</th>
<th>Protein (%)</th>
<th>Lipid (%)</th>
<th>Energy (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>690</td>
<td>86.6</td>
<td>8.8</td>
<td>0.1</td>
<td>19.5</td>
</tr>
<tr>
<td>26</td>
<td>880</td>
<td>86.8</td>
<td>9.2</td>
<td>1.5</td>
<td>123.6</td>
</tr>
<tr>
<td>28</td>
<td>1160</td>
<td>84.6</td>
<td>9.6</td>
<td>5</td>
<td>326.2</td>
</tr>
<tr>
<td>40</td>
<td>3450</td>
<td>74.0</td>
<td>12</td>
<td>15.3</td>
<td>3152.4</td>
</tr>
<tr>
<td>2 months</td>
<td>5450</td>
<td>71.4</td>
<td>11.4</td>
<td>25</td>
<td>9866</td>
</tr>
</tbody>
</table>

Ziegler, E. Growth, 1976
Nutritional Mediation of Illness Severity

- As Total energy intake during the first 7 days of life increased in critically ill infants, the Odds Ratio of such adverse outcomes as NEC, late onset sepsis, BPD and NDI decreased by approximately 2% for each 1kcal/kg/d of total energy intake.

25 wk

term
First week protein and energy intake and neurodevelopmental outcome @18 months

- Retrospective study of 124 ELBW infants at 18 months CA

In-hospital growth velocity and neurodevelopmental outcome

- Cohort study, 600 infants with birth weight 501 to 1000g

ENERGY REQUIREMENTS

- 120 CAL/KG/D FOR GROWTH IF FED ENTERALLY.
- IF ON TPN, POSITIVE NITROGEN BALANCE CAN BE ATTAINED WITH 60 CAL/KG/D WITH ABOUT 2.5 G/KG/D OF PROTEIN.
- MINIMAL CALORIC INTAKE FOR WEIGHT GAIN IS ABOUT 80 CAL/KG/D IF ON TPN.
## High vs. Low Amino Acid Intake and Glucose/Insulin

<table>
<thead>
<tr>
<th></th>
<th>Low amino acids</th>
<th>High amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose, mmol/L</strong></td>
<td>6.2 ± 0.7 (113 ± 13)</td>
<td>6.9 ± 0.8 (125 ± 14)</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin, pmol/L</strong></td>
<td>75 ± 13 (10.5 ± 1.9)</td>
<td>139 ± 23 (19.3 ± 3.1)*</td>
</tr>
<tr>
<td>(µU/mL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values expressed as mean ± SEM.

* Significant difference between groups, \( p < 0.05 \).
Delayed TPN, Hyperglycemia and Hyperkalemia

Delayed TPN

- Low Leucine, arginine
- Other amino acids

Insulin

Glucose —> K⁺
“Intravenous Lipids Are Poison”

Anonymous Neonatologist—Early 1980’s
Nutritional practices in the neonatal intensive care unit: analysis of a 2006 neonatal nutrition survey.
In 80-90% of the units, sepsis, hemodynamic failure, thrombocytopenia, disseminated intravascular coagulation and hyperbilirubinemia were considered to be relative or absolute contraindications.
Rationale for Providing Lipids Early

- In utero lipid supply is approximately 2.5-3.0 grams/kg/d
- Essential Fatty Acid (EFA) status in early infancy is low and is rapidly exacerbated with lipid free nutrition.
- Long Chain Polyunsaturated Fatty Acid (LCPUFA) derivatives from EFAs are important in brain and retinal development.
- Prevention of catabolism and protein sparing.
## Biochemical EFA Deficiency in Prematures: Holman Index

<table>
<thead>
<tr>
<th>Linoleic acid intake (g/kg/d)</th>
<th>NO IV Lipid RDS + NO Feed</th>
<th>NO IV Lipid RDS + Feed +</th>
<th>IV Lipid + RDS + NO Feed</th>
<th>NO IV Lipid NO RDS Feed +</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.02</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0.20</td>
<td>0.80</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0.50</td>
<td>1.1</td>
<td>1.7</td>
</tr>
</tbody>
</table>

### Triene:Tetraene Ratio > 0.2

<table>
<thead>
<tr>
<th>Linoleic acid intake (g/kg/d)</th>
<th>NO IV Lipid RDS + NO Feed</th>
<th>NO IV Lipid RDS + Feed +</th>
<th>IV Lipid + RDS + NO Feed</th>
<th>NO IV Lipid NO RDS Feed +</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 (5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>3 (15%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>16 (80%)</td>
<td>4 (13%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Birth weight 1.35 kg, gestational age 31 wk; IV Lipid + = 1 - 3 g/kg/d

Gutcher, AJCN 1991; 54:1024
Calculation (assume 1kg baby)

- Need total of 80 Kcal/Kg/d for growth
- Glucose:
  - 8mg/kg/min ~ 39 Kcal
- Amino Acids:
  - 3 gm/Kg/d = 12 Kcal
- Lipids:
  - Still need ~30 Kcal for 80 total
    - 30 kcal X cc/2.2 Kcal X 0.2 gm/cc = 2.7 gm/d
Practical preterm parenteral nutrition: Systematic literature review and recommendations for practice

S. Uthaya *, N. Modi

Imperial College London, UK
Chelsea Westminster Hospital NHS Foundation Trust, London, UK

Keywords:
Parenteral nutrition
Amino acids
Prematurity
Newborn intensive care
Nutrition
Infant
Intravenous lipids

ABSTRACT

Current practice in relation to the prescribing, compounding and administration of parenteral nutrition for extremely preterm infants is inconsistent and based on largely historical evidence. Increasingly there are calls for more 'aggressive' nutritional interventions to prevent 'postnatal growth failure'. However the evidence base for these recommendations is weak, and there are no long-term studies examining the impact of such practices. Here we summarise the evidence for preterm parenteral nutrition interventions. We suggest principles to guide practice based on evidence from a systematic search and review of evidence to date, and recommend actions necessary to advance the understanding of this important aspect of preterm care.

Amino acids should be commenced as soon as possible after birth and no later than 24 h. It is safe to commence 2–3.5 g/kg/day of amino acids from day one. The benefits of higher amino acid intakes on short or long-term outcomes remain to be established. Lipid should be commenced on day one. There is currently no evidence to support the routine use of third generation lipids such as SMOF Lipid. Carbohydrate intake may be commenced at 8–10 g/kg/day and may be increased depending on glucose control. There is no evidence for preferring the use of insulin to reducing glucose intake to manage hyperglycaemia.
Safety and Efficacy of Early Parenteral Lipid and High-Dose Amino Acid Administration to Very Low Birth Weight Infants

Hester Vlaardingerbroek, MD, PhD, Marijn J. Vermeulen, MD, PhD, Denise Rook, MD, PhD, Chris H. P. van den Akker, MD, PhD, Kristien Dorst, Josias L. Wattimena, Andras Vermes, PharmD, PhD, Henk Schierbeek, PhD, and Johannes B. van Goudoever, MD, PhD

Objective To assess the efficacy and safety of early parenteral lipid and high-dose amino acid (AA) administration from birth onwards in very low birth weight (VLBW, birth weight <1500 g) infants.

Study design VLBW infants (n = 144; birth weight 862 ± 218 g; gestational age 27.4 ± 2.2 weeks) were randomized to receive 2.4 g of AA kg⁻¹·d⁻¹ (control group), or 2.4 g AA kg⁻¹·d⁻¹ plus 2-3 g lipids kg⁻¹·d⁻¹ (AA + lipid group), or 3.6 g AA kg⁻¹·d⁻¹ plus 2-3 g lipids kg⁻¹·d⁻¹ (high AA + lipid group) from birth onwards. The primary outcome was nitrogen balance. The secondary outcomes were biochemical variables, urea rate of appearance, growth rates, and clinical outcome.

Results The nitrogen balance on day 2 was significantly greater in both intervention groups compared with the control group. Greater amounts of AA administration did not further improve nitrogen balance compared with standard AA dose plus lipids and was associated with high plasma urea concentrations and high rates of urea appearance. No differences in other biochemical variables, growth, or clinical outcomes were observed.

Conclusions In VLBW infants, the administration of parenteral AA combined with lipids from birth onwards improved conditions for anabolism and growth, as shown by improved nitrogen balance. Greater levels of AA administration did not further improve the nitrogen balance but led to increased AA oxidation. Early lipid initiation and high-dose AA were well tolerated. (J Pediatr 2013;163:638-44).
WHEN TO START LIPIDS

• ASAP—As Soon As Possible. No studies that show problems starting at 3.0 gm/kg/d.

• USUALLY NOT MORE THAN 3.0 GM/KG/D NEED PROVIDED.

• HYPERLIPIDEMIA TOUGH TO MONITOR

• PROLONGED INFUSIONS USUALLY SAFE (<0.2 GM/KG/HR).
Monitoring Triglycerides

- Different norms are recommended by different authors (e.g. 100-150, <200 mg/dl, etc.)
- Is this efficacious and /or realistic?
Parenteral Nutrition: Where Are We?

• Still a ways to go:
  – Amino acid composition not optimal
  – Upper limit of Amino Acids unclear
  – Lipid composition not optimal
  – Use of multi-source lipids may be beneficial
  – Personalization is difficult
  – Many complications
AGA 27 week: APGARS 3 and 5, UA and UV catheters in place, On mechanical ventilation and prophylactic indomethacin

- Can we feed this baby using the GI tract?
- What are the consequences of not feeding this baby?
- How do we feed this baby?
Dr. Elsie Widdowson (1906-2000)

The suckled pig’s duodenum gains 42% of its weight in the first 24 hours after birth.

Plasma [GI Hormone] in Premature Infants

Liver after 7 days of TPN vs. Enteral Feeding in Piglets


H & E

ORO fat Staining

Diastase glycogen staining
Effect of Total Parenteral Nutrition (TPN) in Mice

Barrier Function: loss of Epithelial Integrity

Bacterial or toxin Translocation

INTESTINAL EPITHELIUM

IL-8

SIRS

LOCAL OR DISTAL ORGAN INJURY
- NEC
- Chronic lung disease
- Neuro-developmental delays
Effect of GI Priming on Intestinal Permeability

Permeability (Lactulose/mannitol ratio $\times 10^{-2}$)

Birth weight 1 kg
Gestational age 28 wk

- GI Priming, day 4-14
- TPN only to day 15

10 days

Shulman et al, Pediatr Res 1998;44:5...
You are on call at 2am. Nurse reports that this baby who is being fed 2 ml breast milk every 3 hours is having 2 cc gastric residuals. What do you do?

- Tell the nurse not to bother you at 2am?
- Stop all feedings?
- Ask about the physical exam and perhaps examine baby yourself?
Checking or Not Checking Gastric Residuals

### Table 2. Specific Outcomes Measured. (Mean ± SD)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Check GR (N=30)</th>
<th>No Check GR (N=31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteral intake 2 weeks after birth</td>
<td>106.73±53.74</td>
<td>112.20±42.81</td>
<td>0.66</td>
</tr>
<tr>
<td>Enteral intake 3 weeks after birth</td>
<td>134.20±39.44</td>
<td>141.00±29.29</td>
<td>0.41</td>
</tr>
<tr>
<td>Day of life of full enteral intake at 120 ml/kg/d</td>
<td>16.8±12.4</td>
<td>14.3±12.5</td>
<td>0.29</td>
</tr>
<tr>
<td>Day of life of full enteral intake at 150 ml/kg/d</td>
<td>28.1±3.9</td>
<td>22.3±11.7</td>
<td>0.19</td>
</tr>
<tr>
<td>Percentage of Change of Growth Parameters:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight at 3 weeks</td>
<td>23.8±19</td>
<td>23.6±21</td>
<td>0.98</td>
</tr>
<tr>
<td>Length at 3 weeks</td>
<td>7.1±5</td>
<td>6.4±5.5</td>
<td>0.58</td>
</tr>
<tr>
<td>Head circumference at 3 weeks</td>
<td>8.6±5.9</td>
<td>7.8±3.9</td>
<td>0.51</td>
</tr>
<tr>
<td>Day of life when PN was discontinued</td>
<td>15.1±11</td>
<td>13.8±5.9</td>
<td>0.57</td>
</tr>
<tr>
<td>Day of life when central access was discontinued</td>
<td>21.3±20.7</td>
<td>15.6±5.9</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Murgas Torrazzo, R., J. Perinatology, 2014
Checking or Not Checking Gastric Residuals

Table 2. Clinical Complications Measured. (%)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Check GR (N=30)</th>
<th>No Check GR (N=31)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNALD</td>
<td>4/30 (13.3)</td>
<td>4/31 (12.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>SEPSIS</td>
<td>11/30 (36.7)</td>
<td>9/31 (29)</td>
<td>0.59</td>
</tr>
<tr>
<td>NEC</td>
<td>3/30 (10)</td>
<td>1/30 (3.2)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Do You Keep Feeding?

- Indomethacin for Ductus?
- Indomethacin for IVH Prophylaxis?
- Blood transufusion?
Superior Mesenteric Artery Flow

Niinikoshi, J. Nutrition, 2004
Enteral Feeding during Indomethacin and Ibuprofen Treatment of a Patent Ductus Arteriosus

Ronald Clyman, MD[^1][^2], Andrea Wickremasinghe, MD[^1][^2], Nami Jhaveri, MD[^1][^2], Denise C. Hassinger, MD[^3], Joshua T. Attridge, MD[^4], Ulana Sanocka, MD[^5], Richard Polin, MD[^5], Maria Gillam-Krakauer, MD[^6], Jeff Reese, MD[^6], Mark Mammel, MD[^7], Robert Couser, MD[^7], Neil Mulrooney, MD[^7], Toby D. Yanowitz, MD[^8], Matthew Derrick, MD[^9], Priya Jegatheesan, MD[^10], Michele Walsh, MD[^11], Alan Fujii, MD[^12], Nicolas Porta, MD[^13], William A. Carey, MD[^14], and Jonathan R. Swanson, MD[^3], on behalf of the Ductus Arteriosus Feed or Fast with Indomethacin or Ibuprofen (DAFFII) Investigators[^*]

**Objective** To test the hypothesis that infants who are just being introduced to enteral feedings will advance to full enteral nutrition at a faster rate if they receive “trophic” (15 mL/kg/d) enteral feedings while receiving indomethacin or ibuprofen treatment for patent ductus arteriosus.

**Study design** Infants were eligible for the study if they were 23\(^{1/7}\) to 36\(^{6/7}\) weeks' gestation, weighed 401-1250 g at birth, and had maximum enteral volumes of 60 mL/kg/d, and were about to be treated with indomethacin or ibuprofen. A standardized “feeding advance regimen” and guidelines for managing feeding intolerance were followed at each site (N = 13).

**Results** Infants (N = 177, 26.3 ± 1.9 weeks’ mean ± SD gestation) were randomized at 6.5 ± 3.9 days to receive “trophic” feeds (“feeding” group, n = 81: indomethacin 80%, ibuprofen 20%) or no feeds (“fasting [nil per os]” group, n = 96: indomethacin 75%, ibuprofen 25%) during the drug administration period. Maximum daily enteral volumes before study entry were 14 ± 15 mL/kg/d. After drug treatment, infants randomized to the “feeding” arm required fewer days to reach the study’s feeding volume end point (120 mL/kg/d). Although the enteral feeding end point was reached at an earlier postnatal age, the age at which central venous lines were removed did not differ between the two groups. There were no differences between the 2 groups in the incidence of infection, necrotizing enterocolitis, spontaneous intestinal perforation, or other neonatal morbidities.

**Conclusion** Infants required less time to reach the feeding volume end point if they were given “trophic” enteral feedings when they received indomethacin or ibuprofen treatments. (*J Pediatr* 2013; 16: 228-33).
Specific Circumstances: Hypothermia for HIE

• Why not?
• History of major advantages (decreased mortality, inflammatory responses, etc.) to feeding under high stress conditions (burns, trauma, etc.)
• Enteral feeding in Scandinavia—”safe”.

Present and Future: Personalized Nutrition

The "Omics" Future

Microbiome/Metabolome/Genome/Proteome/Transcriptome

Healthy Eating Pyramid

The "Omics" Future

Personalized Food Menu
Breast milk microbes
Over time

Hunt, et al. PlosOne
2011

Figure 1. The community composition of the 15 most abundant bacterial genera in each of 3 milk samples from 16 subjects was diverse. The communities observed were found to be reasonably complex, and while consistent in composition over time for some subjects, a great deal of variation was observed over time in the samples of others.
doi:10.1371/journal.pone.0021313.g001
Microbial Phyla in the Stools of Breast vs. Formula Fed Neonates

A Breastfed

- **Un_sub_classified**: 7.0%
- **Firmicutes**: 9.8%
- **Bacteroidetes**: 19.6%
- **Proteobacteria**: 26.4%
- **Actinobacteria**: 37.1%

B Formula-fed

- **Verrucomicrobia**: 3.2%
- **Proteobacteria**: 11.1%
- **Actinobacteria**: 46.4%
- **Firmicutes**: 35.1%

Un_sub_classified 3.3%

Evidence-Based Guidelines for Optimization of Nutrition for the Very Low Birthweight Infant
Roberto Murgas Torrazza and Josef Neu
Neoreviews 2013;14:e340
DOI: 10.1542/neo.14-7-e340

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://neoreviews.aappublications.org/content/14/7/e340

Scientifically Based Strategies for Enteral Feeding in Premature Infants
Leslie A. Parker, Josef Neu, Roberto Murgas Torrazza and Yuefeng Li
Neoreviews 2013;14:e350
DOI: 10.1542/neo.14-7-e350
Summary

• Early nutrition in premature babies can be safe and efficacious and may prevent significant morbidity.
• Many of the dogmas that have prevented rapid incorporation of early nutrition have either been disproved, not based on fact or weak.
• Personalization of nutrition for the neonate may be possible.