The Management of Lipids During the Neonatal Period

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Associate Director, NICU, Department of Neonatology
Director for Cross-Disciplinary Research Partnerships,
Division of Translational Research
Beth Israel Deaconess Medical Center, Boston MA
I have the following financial relationships to disclose:
Consultant for: Mead Johnson, Abbott, Nestle
Grant/Research Support from: Abbott Nutritionals, Alcresta, Gilead, Hood Foundation
Scientific Advisory Board: Alcresta

I will be discussing the scientific literature of non-FDA approved lipid emulsions.
Objectives

① Review current rationale and recommendations for lipid delivery
② Discuss fatty acid requirements during fetal development
③ Discuss the current scientific literature in defining the therapeutic role of fatty acids in critically ill infants
④ Identify challenges and postulate potential strategies to optimize lipid delivery and postnatal fatty acid utilization
Lipid: Definition

• Organic compound that is readily soluble in nonpolar solvent but not in polar solvent (e.g. water)

• Major functions
  – Nutritional: energy, gluconeogenesis, essential fatty acids
  – Biologic: structural component of cell membrane, cell signaling, regulation of inflammation, organogenesis, immune reactivity

• Examples: sterols, cholesterol, monoglycerides, diglycerides, triglycerides, and phospholipids
Delivery of Nutrition in the Preterm Infant: Parenteral & Enteral Phases

Figure 1. Proportion of infants on full enteral feedings versus those still receiving at least partial parenteral nutrition.

History of IV Lipid Emulsions

William Courten
IV Olive Oil infusions in dogs

William Harvey
discovery of the circulation formed the basis for IV infusions

Philos Trans R Soc
27:485-500, 1712

1628 | 1679
Experiments and Observations of the Effects of several sorts of Poisons upon Animals, &c. Made at Montpellier in the Years 1678 and 1679, by the late William Courten Esq; Communicated by Dr. Hans Sloane, R. S. Secr. Translated from the Latin MS.

February the 20th 1679, we injected into the Crural Vein of a little Dog, half an Ounce of warm Oil of Olives, which we did with a great deal of difficulty, and very slowly, by reason of the smallness of the Vein and thickness of the Liquor. For half a quarter of an Hour that we were injecting the Liquor, the Dog did not seem to be uneasy or out of order; but after that, he barked, cried, looked dejected, and fell presently into a deep Apoplexy; so that his Limbs were deprived of Sensibility and Motion, and were flexible any way at pleasure; his Respiration still continuing very strong, with a shorting and wheezing, and a thick watery Humour flowing in great quantity out of his Mouth, which was sometimes mixt with Blood. He lost all External Sense; his Eyes, tho' they continued open, were not sensible of any Objects that were put to them; and we touched and rubbed the Cornea (as sensible a part as it is) without any more sign of his being sensible of it than if he had been dead. His Eye-lids notwithstanding had a Convulsive Motion; his Hearing was quite lost; and his Feeling, tho' at first he seemed to have some small Sense of it when we touched his Wound, yet afterwards it was so dull, that we pinched his Claws and Flew with Pincers, and bored Holes thro' his Ears, without his moving or seeming to be the least sensible of it. It is worth observing, that in the midst of his Sleep, being sometimes seiz'd with a Convulsive Motion of his Diaphragme and other Muscles that help Respiration, he would bark strongly as if he were awake, and in a little time would be quiet again: So that in less than a quarter of an Hour his Rest would be disturbed 3 or 4 times with this violent Barking. But considering this more attentively, we found that at the very time he barked, he was as void of Sense as before; for we could neither make him Bark, nor leave off Barking, by either beating or pricking him; but in a little time he would leave off of himself, and return to it again some time after. Thus in three Hours after the Injection, spent in Sleeping and Barking, he dyed; and having opened his Body after he was dead, we found the Bronchia of the Lungs filled with a thick Froth.

A few Days after we injected a larger quantity, viz. an Ounce of Oil of Olives into the Jugular Vein of a Dog, which suffocated him the same Moment. Afterwards the same quantity of Oil of Olives, being injected into the Jugular Vein of a Dog, killed him in an Hours time. He was seiz'd with a great Sleepiness, Snorting and Wheezing, and a bloody Water run plentifully out of his Mouth. In this Dog, tho' he did not dye immediately, we did not observe the Barking as in the former; But in all that were suffocated by Oil, we found their Lungs filled with a very thick Froth.
Philos Trans R Soc 27:485-500, 1712

William Courten (France) IV Olive Oil infusions in dogs

William Harvey (England) discovery of the circulation formed the basis for IV infusions

Arvid Wretlind (Sweden) soybean oil using egg yolk phospholipids as the emulsifying agent (IntraLipid)

- Various composition tested: castor oil, olive oil, cottonseed oil.
- Side effects - nausea, vomiting and fever, liver damage, jaundice, bleeding tendency.

- Structured lipids
- MCT: LCT Ratios
- LCPUFAs
- No new lipid emulsion approved by the FDA
Lipid Emulsion Destabilization

adapted from: Prof. Dr. Stefan Mühlebach, Swissmedic

reversible

irreversible

Lecithin emulsifier
MDD < 0.5 μm

USP <729> Droplet Methods:
DLS/SLS and LE/SPOS
Globule Size Distribution:
Key Regions Governing Stability

MDS via DLS and LDT via LE/SPOS (PF 2004;30:2244-53)

USP <729>
PFAT > 5 um < 0.05%

MDS via DLS and LDT via LE/SPOS (PF 2004;30:2244-53)
## Incidence of Hypertriglyceridemia in Critically Ill Neonates Receiving Lipid Injectable Emulsions in Glass Versus Plastic Containers: A Retrospective Analysis

*J Pediatr 2008;152:232-6*

Camilia R. Martin, MD, Gregory J. Dumas, RPh, Claire Shoae, RD, Zheng Zheng, MPH, Brenda MacKinnon, RN, Issa Al-Aweel, MS, Bruce R. Bistrian, MD, PhD, DeWayne M. Pursley, MD, and David F. Driscoll, PhD

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>GA, weeks</td>
<td>28.4 ± 2.4</td>
<td>29.1 ± 2.3</td>
<td>0.096</td>
</tr>
<tr>
<td>BW, g</td>
<td>1093 ± 321</td>
<td>1234 ± 454</td>
<td>0.048</td>
</tr>
<tr>
<td>Fat Dose, g/kg/day</td>
<td>1.32 ± 0.46</td>
<td>1.39 ± 0.56</td>
<td>0.465</td>
</tr>
<tr>
<td>TG Level, mg/dL</td>
<td>90 ± 43</td>
<td>120 ± 86</td>
<td>0.012</td>
</tr>
<tr>
<td>Hyper TG, incidence</td>
<td>3/50 or 6%</td>
<td>19/72 or 26%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Time of TG, days</td>
<td>5.4 ± 2.1</td>
<td>5.4 ± 1.7</td>
<td>0.974</td>
</tr>
<tr>
<td>TBili, mg/dL</td>
<td>4.9 ± 2.1</td>
<td>4.9 ± 2.4</td>
<td>0.889</td>
</tr>
</tbody>
</table>
February 21, 2007

Dear Baxter Customer,

Thank you for your inquiry regarding globule size distribution of INTRALIPID IV Fat Emulsion. Only recently has globule size distribution (GSD) been proposed to the USP as a characterization of IV fat emulsions. The USP<729> proposed limit for the large diameter tail of the globule size distribution, expressed as the volume-weighted percentage of fat residing in globules larger than 5 microns (PFAT5), is that it should not exceed 0.05% of the total lipid present. Concerns regarding fat globule size relate to potential/theoretical stability and safety issues.

Upon learning of the USP proposal to add PFAT5 to the standard testing and to set a limit of PFAT5< 0.05%, Baxter and Fresenius Kabi initiated several actions.

During the course of implementing ongoing process improvements, Fresenius Kabi now manufactures INTRALIPID IV Fat Emulsion in plastic container with a PFAT5 < 0.05%. INTRALIPID 20% customers began receiving this product in the September 2006 timeframe. All INTRALIPID IV Fat Emulsion products were transitioned by the end of 2006.
Current Lipid Emulsions

Table 1. Composition of Intravenous Lipids

<table>
<thead>
<tr>
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Omega-6 (linoleic)

Omega-3 (linolenic)

Deshpande and Simmer Current Opin in Clin Nutr and Met Care 2011

Innis. NeoReviews. 2002;3(3):e49
Essential Fatty Acid Deficiency

- Short delay of even 3-7 days can lead to biochemical EFA deficiency

- EFAD deficiency syndrome: dermatitis, alopecia, thrombocytopenia, susceptibility to bacterial infection and failure to thrive

- Increases free radical formation

- Can be prevented with as little as 0.5 to 1.0 gm/kg/day
Essential Fatty Acid Deficiency

Fig. 2 Appearance of skin of 6-week-old twins. A, Given a skim milk mixture lacking linoleic acid. B, Given a milk mixture containing linoleic acid.

Lipids Primary in Supporting Gluconeogenesis

Gluconeogenesis
(N=14, 993 +/- 36g, 27 +/- 1w GA)

Withdrawal of Intralipid®

Withdrawal of TrophAmine®

Mean ± SE

Alternate Substrates Maintain Blood Glucose

Glucose 10.8/6.1/3.1 mg/kg/min
AA 2.2 g/kg/d
Lipid 1.6 g/kg/d

(N=20, 27 +/- 0.2w GA, 996 +/- 28g)

Fats: High Energy Source

Calorie Scale: Fats pack the most energy (calories) per unit weight

- **Carbohydrates**: 4 Calories per Gram
- **Protein**: 4 Calories per Gram
- **Fats**: 9 Calories per gram

Efficient in ATP production, preferred substrate in select tissues

http://dtc.ucsf.edu/
Preterm infants have very limited endogenous lipid stores.

Essential component of parenteral nutrition:
- Serves as a source of Linoleic Acid; Necessary to **prevent essential fatty acid deficiency** (0.5 – 1.0 gm/k/day)
- Important source for **gluconeogenesis**; which, ultimately may also reduce need for increased glucose infusion rates
- Meets **high energy** needs: High caloric source at 9 kcal/gm

Step-wise advancement starting at 1.0 gm/k/day to goal of 3.0 gm/k/day

Monitor triglyceride levels

20% preparation recommended for neonates (lower PL/TG ratio); improved tolerance over 10% solutions (decrease risk of hypertriglyceridemia, hypercholesterolemia, hypephospholipidemia)
Free Fatty Acids and/or Hypertriglyceridemia does NOT Influence Total or Free Bilirubin Levels

Rubin M et al. JPGN 1995
Pulmonary Effects of Lipid Emulsions

Lipid Accumulation

- Older studies, 10% emulsions
- Noted in preterm infants NOT receiving IL
- *General defect* in handling fats?

Vascular Resistance

- Acute change – metabolic vs obstructive (none hyperlipemic)
- All clinical improved - ? Clinical significance


Prasertsom et al, Archives of Disease in Childhood 1996; 74: F95-F98
IL and Sepsis

ASSOCIATION OF INTRAVENOUS LIPID EMULSION AND COAGULASE-NEGATIVE STAPHYLOCOCCAL BACTEREMIA IN NEONATAL INTENSIVE CARE UNITS

Jonathan Freeman, M.D., Sc.D., Donald A. Goldmann, M.D., Nancy E. Smith, M.S., David G. Sidebottom, M.D., Michael F. Epstein, M.D., and Richard Platt, M.D., M.S.


Fischer et al., Lancet 1980
### Intralipid for the Preterm Infant

#### Table: Co-Morbidity and Hold Lipids?

<table>
<thead>
<tr>
<th>Co-Morbidity</th>
<th>Hold Lipids?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperbilirubinemia</td>
<td>No</td>
</tr>
<tr>
<td>Lung Disease</td>
<td>No</td>
</tr>
<tr>
<td>Sepsis</td>
<td>No</td>
</tr>
<tr>
<td>Surgical Bowel</td>
<td>1 gm/k/d</td>
</tr>
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</table>

#### Fats:
- Essential to balanced diet and cellular components
- Prevention of EFAD
- High energy source
- Driver of gluconeogenesis

#### Hypertriglyceridemia:
- PVR
- Immune reactivity
- Other?

Intralipid is our only option and we must provide; however, we can do better!
Next Generation of Lipid Emulsions

Providing Adequate Nutrition

Promoting Optimal Development
Fatty Acid: Definitions

- Long hydrocarbon chain capped by a **carboxyl group** (COOH)

**Saturated**: Saturated with hydrogens, every carbon links with the maximum number of hydrogens, thus **all single bonds**

**Unsaturated**: Not every carbon links with the maximum number of hydrogens, thus some carbon-carbon links are **double bonds**
Fatty Acid: Nomenclature

1. Total number of carbons (c)
2. Total number of double bonds
3. Number of carbon from the terminal methyl end with the first double bond

Linolenic acid, an omega-3 fatty acid
(the omega carbon atom is shown in blue)

18:3 (n-3)

1 2 3
In Utero Delivery of Fatty Acids: Adipose and Neural Tissues Major Targets

Haggarty 2010
No Replacement of In Utero Delivery of Fatty Acids After Preterm Birth
DHA Levels Rapidly Decline in the First Postnatal Week


Median DHA levels at birth in **TERM** infants

Median DHA levels at birth in **PRETERM** infants

Median DHA levels present throughout the 3rd trimester

LA & AA Levels Rapidly Altered in the First Postnatal Week

Median LA levels observed in TERM infants

Median AA levels present throughout the 3rd trimester

Median LA levels present throughout the 3rd trimester

Median AA levels at birth in PRETERM infants

Median LA levels observed in PRETERM infants

Median AA levels observed in TERM infants

Current Lipid Emulsions

Table 1 Oil combinations used to formulate currently available lipid emulsions (percentage of lipid)

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<tr>
<td>Fish oil</td>
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ND, no data.

Deshpande and Simmer Current Opin in Clin Nutr and Met Care 2011

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soy/olive, 25/75 v/v; MCT/LCT, 50/50 v/v

Innis. NeoReviews. 2002;3(3):e49

Omega-6 (linoleic)
Omega-3 (linolenic)
Factors Impacting Fatty Acid Levels

- Enzyme activity
- Utilization rate
- Amount of substrate
Current Nutritional Practices Inadequate

Current Nutritional Strategies Fail to Deliver Fetal Fatty Acid Requirements

Inevitable DHA Deficit

Lapillonne 2010
Biologic Importance of Fatty Acids

DHA and polyunsaturated fatty acids (PUFAs) are important in:

1. Maintaining the structure of the cell – fluidity & function
2. Regulating the production of proteins
Accruing Evidence for Fatty Acids & Neonatal Health

- Bronchopulmonary Dysplasia
- Late-Onset Sepsis
- Neurodevelopment & WMI
- Intestinal Development & NEC
- Retinopathy of Prematurity

① Inflammation
② Organogenesis
③ Immune function
④ Angiogenesis
⑤ Neurodevelopment
Low DHA Levels are Linked to the Development of Chronic Lung Disease (CLD)

Mean DHA levels for all infants

- No CLD
- + CLD

Postnatal week (birth = week 0)

3
4
5
6
7

0
1
2
3
4

(n=54)
(n=63)
(n=56)
(n=34)
(n=35)

Maternal DHA and CLD

High-Dose Docosahexaenoic Acid Supplementation of Preterm Infants: Respiratory and Allergy Outcomes

Brett J. Manley, Maria Makrides, Carmel T. Collins, Andrew J. McPhee, Robert A. Gibson, Philip Ryan, Thomas R. Sullivan, Peter G. Davis and for the DINO Steering Committee

*Pediatrics* 2011;128:S71; originally published online June 27, 2011; DOI: 10.1542/peds.2010-2405

<table>
<thead>
<tr>
<th>TABLE 1 Respiratory Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Infants</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Oxygen at 36 weeks⁵</td>
</tr>
<tr>
<td>Birth weight &lt;1250 g⁷</td>
</tr>
<tr>
<td>Birth weight ≥1250 g⁷</td>
</tr>
<tr>
<td>Male infants⁹</td>
</tr>
<tr>
<td>Female infants⁹</td>
</tr>
</tbody>
</table>
Fatty Acid Metabolites
DHA & AA Metabolites Attenuate Lung Injury

Room Air

Hyperoxia

Increased Oxygen

Resolvin D1 (RvD1)

Lipoxin A4 (LXA4)

RvD1 & LXA4

Histology (H&E): 200x

Presented PAS 2013 Platform; manuscript submitted

© Martin-Freedman Laboratory, Beth Israel Deaconess Medical Center
Select Fatty Acids & Ratios Associated with Increased Risk of CLD & Late-Onset Sepsis

<table>
<thead>
<tr>
<th>CLD</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>0.9 (0.7, 1.1)</td>
<td>0.4</td>
</tr>
<tr>
<td>AA</td>
<td>0.9 (0.6, 1.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>DHA</td>
<td>2.5 (1.3, 5.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>LA: DHA</td>
<td>8.6 (1.4, 53.1)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Late-onset sepsis</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>0.8 (0.7, 0.96)</td>
<td>0.02</td>
</tr>
<tr>
<td>AA</td>
<td>1.4 (1.1, 1.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>DHA</td>
<td>1.4 (1.0, 2.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>LA: DHA</td>
<td>4.6 (1.5, 14.1)</td>
<td>0.007</td>
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Models adjusted for gestational age, gender, growth restriction, severity of illness, total Intralipid intake

Fatty Acids & Neural Tissue Development
DHA Affects Membrane Fluidity & Increasing Anchoring Sites for Signaling Proteins

http://upload.wikimedia.org/wikipedia/commons/thumb/2/2e/Lipid_unsaturation_effect.svg/350px-Lipid_unsaturation_effect.svg.png

Wassall and Stillwell Biochimic et Biophysica Acta 2009
DHA Signaling

DHA

15-LOX-1

NPD1

NPD1 = Neuroprotectin D1
Protection against oxidative stress triggered apoptosis

MAPK

BDNF

BDNF = Brain Derived Neurotrophic Factor
Brain Derived Neurotropin Factor & Akt Activation

Akt Activates CREB and mTORs

CREB & mTOR critical for Neurodevelopment

CREB
Regulates gene expression for proteins involved in:
- Growth & survival, Neuroprotectin, Synaptic plasticity

Lonze and Ginty Neuron 2002

mTOR
Regulates protein translation of synaptic proteins:
- actin organization, cell size & survival, autophagy, mitochondrogenesis

Fretham J Nutrition 2013
Fatty Acids & Intestinal Health

PPARs

Microbiome

1

2

3

Cell membrane phospholipids

Inflammatory eicosanoids

Resolvins

n-3 PUFAs

TLR4

4

PPARs

Signal transduction

NF-κB

Nucleus

↓ Cytokines

↓ Adhesion molecules

↓ Intestinal inflammation

PPAR=Peroxisome proliferator-activated receptor

Wahli W. Journal of Internal Medicine 2008;263:613-619
PUFAs & Necrotizing Enterocolitis

Decrease PAFR and TLR4 gene expression
Omega-3 & Retinopathy of Prematurity

Vasoobliteration / Neovascularization:

- $\omega-6$: 21.5 / 9
- $\omega-3$: 13.7 / 5.7

Mouse pups exposed to 75% O2 from P7 – P12

Connor et al. Nature Medicine, 2007
Early Alterations in Fatty Acids Occur During a Critical Period of Immune & Organ Development

1. Current delivery of nutrition fails to maintain DHA levels
2. This failure associated with neonatal morbidities
Improving Lipid Delivery in the Preterm Infant
Defining the Needed Changes
Median DHA levels at birth in **TERM** infants

Median DHA levels at birth in **PRETERM** infants

Median DHA levels present throughout the 3rd trimester

DHA Deficit

Parenteral phase

Enteral phase
## Current Lipid Emulsions

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<td>10</td>
<td>15</td>
<td>ND</td>
<td>100</td>
</tr>
</tbody>
</table>

ND, no data.

Deshpande and Simmer Current Opin in Clin Nutr and Met Care 2011

### Omega-6 (linoleic)

### Omega-3 (linolenic)

Table 1. Composition of Intravenous Lipids

<table>
<thead>
<tr>
<th></th>
<th>Soy</th>
<th>Soy/Safflower</th>
<th>Soy/Olive</th>
<th>MCT/LCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:0 (%)</td>
<td>11</td>
<td>7.5</td>
<td>13</td>
<td>4.5</td>
</tr>
<tr>
<td>18:0 (%)</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>18:1 (%)</td>
<td>24</td>
<td>18</td>
<td>60</td>
<td>13</td>
</tr>
<tr>
<td>18:2n-6 (%)</td>
<td>55</td>
<td>66</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>18:3n-3 (%)</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Triglyceride (g/L)</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Phospholipid (g/L)</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Glycerol (g/L)</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

soy/olive, 25/75 v/v; MCT/LCT, 50/50 v/v

Innis. NeoReviews. 2002;3(3):e49
Fish-Oil Fat Emulsion Supplementation May Reduce the Risk of Severe Retinopathy in VLBW Infants

AUTHORS: Dorota Pawlik, MD, PhD; Ryszard Lauterbach, MD, PhD; and Ewa Turyk, MD

Departments of Neonatology and Ophthalmology, Jagiellonian University Medical College, Kraków, Poland

- 2010
- Patient population: n=40, BW< 1250g
- Intervention: Composition/blend of Omegaven & Clinoleic
- Control group: Historical
## Fish Oil & Retinopathy of Prematurity

### TABLE 2: Demographic and Clinical Characteristics of Patients in the Experimental and Historical Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Experimental Group (N = 40)</th>
<th>Historical Group (N = 44)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, median (range), g</td>
<td>920 (570–1250)</td>
<td>940 (670–1250)</td>
<td>.72</td>
</tr>
<tr>
<td>Gestational age, median (range), wk</td>
<td>28 (25–32)</td>
<td>28 (24–32)</td>
<td>.81</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>23 (57.5)</td>
<td>28 (63.5)</td>
<td>.46</td>
</tr>
<tr>
<td>SGA infant, n (%)</td>
<td>8 (20)</td>
<td>7 (15)</td>
<td>.21</td>
</tr>
<tr>
<td>Apgar score, median (range)</td>
<td>7.0 (1–9)</td>
<td>7.0 (1–9)</td>
<td>.73</td>
</tr>
<tr>
<td>CRIB score, mean; median (range)</td>
<td>3.77; 2.0 (0.0–11)</td>
<td>3.72; 3.0 (1–13)</td>
<td>.43</td>
</tr>
<tr>
<td>Antenatal steroids, n (%)</td>
<td>21 (52)</td>
<td>19 (43)</td>
<td>.28</td>
</tr>
<tr>
<td>Mechanical ventilation, mean; median (range), d</td>
<td>9.9; 8.0 (1–30)</td>
<td>13.2; 6.0 (1–52)</td>
<td>.31</td>
</tr>
<tr>
<td>n-CPAP ventilation, mean; median (range), d</td>
<td>16.5; 15.0 (1–43)</td>
<td>15.7; 16.0 (2–34)</td>
<td>.35</td>
</tr>
<tr>
<td>PDA closure, N/n nonsurgical/n surgical</td>
<td>20/11/9</td>
<td>23/13/10</td>
<td>.50</td>
</tr>
<tr>
<td>Sepsis, N/n Gram-positive/n Gram-negative</td>
<td>22/20/3</td>
<td>19/16/3</td>
<td>.38</td>
</tr>
<tr>
<td>IVH, n</td>
<td>9</td>
<td>13</td>
<td>.62</td>
</tr>
<tr>
<td>Cholestasis, n</td>
<td>0</td>
<td>5</td>
<td>.056</td>
</tr>
<tr>
<td>TPN, mean; median (range), d</td>
<td>21.7; 21 (5–55)</td>
<td>22.3; 18.5 (7–91)</td>
<td>.25</td>
</tr>
<tr>
<td>Hospitalization, mean; median (range), d</td>
<td>63.1; 61.5 (25–115)</td>
<td>64.9; 61.5 (26–120)</td>
<td>.28</td>
</tr>
<tr>
<td>BPD, n</td>
<td>9</td>
<td>11</td>
<td>.80</td>
</tr>
<tr>
<td>ROP stage 1 to 3, n</td>
<td>13</td>
<td>16</td>
<td>.81</td>
</tr>
<tr>
<td>ROP laser therapy</td>
<td>3</td>
<td>12</td>
<td>.023</td>
</tr>
</tbody>
</table>
Fish Oil & Fatty Acid Levels

Parenteral Nutrition of Preterm Infants with a Lipid Emulsion Containing 10% Fish Oil: Effect on Plasma Lipids and Long-Chain Polyunsaturated Fatty Acids

Rita D’Ascenzo, et al.
The Journal of Pediatrics
Volume 159, Issue 1, July 2011, Pages 33–38.e1

- 2011
- Patient population: n=47, BW< 1250g
- Intervention:
  - 10% fish oil, 50% medium-chain triacylglycerols, and 40% soybean oil (lipoplus)
  - 50:50 medium-chain triacylglycerols: soybean oil (lipofundin)
Fish Oil & Fatty Acid Levels

- ↑ DHA
- No change in postnatal decline

**A**

- **ARA (mol%)**
- Study Group vs Control Group

**B**

- **DHA (mol%)**
- Study Group vs Control Group

**C**

- **EPA (mol%)**
- 6x ↑ EPA

**D**

- **EPA/ARA ratio**
- Study Group vs Control Group

Enteral Phase of Nutrition

Median DHA levels at birth in **TERM** infants

Median DHA levels at birth in **PRETERM** infants

Median DHA levels present throughout the 3rd trimester

DHA Deficit

**Parenteral phase**

**Enteral phase**

Postnatal Week (Birth = Week 0)
Infants enrolled in the trials were relatively mature and healthy preterm infants. Assessment schedule and methodology, dose and source of supplementation and fatty acid composition of the control formula varied between trials. On pooling of results, no clear long-term benefits or harms were demonstrated for preterm infants receiving LCPUFA-supplemented formula.
On pooling of results, no clear long-term benefits or harms (if growth the only parameter) were demonstrated for preterm infants receiving LCPUFA-supplemented formula.

Schulzke SM, Aptole SK, Simmer K 2011
DHA Supplementation & Cognitive Development

- Randomized, double-blind enteral supplementation
- < 33 weeks of gestation
- High DHA (1% total FA) versus standard (0.3% of total FA)
- Day 2-4 to term
- Outcome: NDI at 18 months

Table 2. Outcomes on Bayley Scales of Infant Development, Second Edition

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>High-/Standard-DHA Diet, No.</th>
<th>Mean Scores (SD)</th>
<th>Unadjusted Mean Difference in Scores (95% CI)</th>
<th>Unadjusted P Value</th>
<th>Adjusted Mean Difference in Scores (95% CI)</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Development Index (MDI) Standardized score</td>
<td>322/335</td>
<td>94.9 (14.5) 93.0 (17.3)</td>
<td>1.9 (−1.0 to 4.7)</td>
<td>.20</td>
<td>1.6 (−1.2 to 4.3)</td>
<td>.26</td>
</tr>
<tr>
<td>Birth weight &lt;1250 g b</td>
<td>147/149</td>
<td>94.8 (15.6) 90.0 (18.4)</td>
<td>4.7 (0.2 to 9.2)</td>
<td>.04</td>
<td>3.8 (−0.5 to 8.0)</td>
<td>.08</td>
</tr>
<tr>
<td>Birth weight ≥1250 g b</td>
<td>175/186</td>
<td>95.1 (13.4) 95.5 (16.1)</td>
<td>−0.4 (−3.7 to 2.9)</td>
<td>.81</td>
<td>−0.40 (−3.7 to 3.0)</td>
<td>.83</td>
</tr>
<tr>
<td>Girls c</td>
<td>149/153</td>
<td>99.1 (13.9) 94.4 (17.5)</td>
<td>4.7 (0.5 to 8.8)</td>
<td>.03</td>
<td>4.5 (0.5 to 8.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Boys c</td>
<td>173/182</td>
<td>91.3 (14.0) 91.9 (17.2)</td>
<td>−0.6 (−4.3 to 3.1)</td>
<td>.76</td>
<td>−1.0 (−4.5 to 2.6)</td>
<td>.60</td>
</tr>
<tr>
<td>Psychomotor Development Index (PDI) Standardized score</td>
<td>322/335</td>
<td>93.1 (16.1) 92.1 (16.3)</td>
<td>0.9 (−1.8 to 3.6)</td>
<td>.50</td>
<td>0.9 (−1.8 to 3.6)</td>
<td>.51</td>
</tr>
<tr>
<td>Birth weight &lt;1250 g d</td>
<td>147/149</td>
<td>91.2 (16.8) 89.6 (17.8)</td>
<td>1.6 (−2.7 to 5.9)</td>
<td>.47</td>
<td>0.9 (−3.3 to 5.1)</td>
<td>.67</td>
</tr>
<tr>
<td>Birth weight ≥1250 g d</td>
<td>175/186</td>
<td>94.7 (15.2) 94.2 (14.8)</td>
<td>0.5 (−2.9 to 3.8)</td>
<td>.78</td>
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<td>.78</td>
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<tr>
<td>Girls e</td>
<td>149/153</td>
<td>94.5 (16.3) 93.9 (16.0)</td>
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<td>.78</td>
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<td>.80</td>
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<td>173/182</td>
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Median DHA levels at birth in **TERM** infants

Median DHA levels at birth in **PRETERM** infants

Median DHA levels present throughout the 3rd trimester

DHA Deficit

? 

Parenteral phase

Enteral phase

Postnatal Week (Birth = Week 0)
Dietary Fats to Fatty Acids

3 Fatty Acids + Glycerol

Carnitine

Fatty acids are oxidized as fuel or reesterified for storage.

Myocyte or adipocyte

CO₂

ATP

Fatty acids enter cells.

Lipoprotein lipase

Lipoprotein lipase, activated by apoC-II in the capillary, releases fatty acids and glycerol.

Chylomicrons move through the lymphatic system and bloodstream to tissues.
Digestion & Absorption of LC-PUFAs

Developmental Pancreatic Insufficiency

Decreased Lipase Production
(Lebenthal and Lee, 1980)

?  

Hydrolysis of TG & Absorption of Fatty Acids
Carbon Length Associated With Absorption Rates

2 Weeks

6 Weeks

P < 0.05 for C14 – C22 at 2 & 6 weeks

CFA was not affected by number of double bonds or omega class.
Maldigestion/Malabsorption of Long Chain Fatty Acids in Premature Infants

CFA for DHA at 2 & 6 weeks (83.4% v 96.2% and 74.9% v 97.4%, respectively)

Presented PAS 2013 Platform

© Martin-Freedman Laboratory, Beth Israel Deaconess Medical Center
Effects of Fat Maldigestion in the Small Bowel of the Neonatal Mouse Pup

Howles et al, Am J Phys 1999
What Dictates Adequate Replacement of Fatty Acids?

① Defining target levels
② Determining dietary balance of n3:n6 fatty acids
③ Ensuring optimal Sn position for absorption & incorporation into cellular phospholipids
④ Optimizing digestion and absorption
⑤ Achieving adequate levels at a tissue, cell, & molecular level
Lipids are a critical component to parenteral nutrition providing a high energy source and an alternative fuel for gluconeogenesis.

Fatty acids are essential for neurodevelopment, cell membrane structure & function, including cell signaling.

LCPUFAs are biomagnified from mother to fetus during the last trimester.

FA profiles are dramatically altered in the *early* postnatal period.

Changes in postnatal FA profiles are linked to neonatal disease and accruing infant and animal data indicate an important role for fatty acids in health.
New strategies need to:
- Consider both the parenteral and enteral periods to maintain birth levels of FA
- Consider the role and balance of all critical FA
- Be introduced early after delivery

Preclinical models and clinical trials should aim to understand:
- Target levels and balance of fatty acids
- Circulating and tissue levels
- Define health outcomes across multiple systems
Acknowledgments

• **Martin-Freedman Lab**
  – Steven D. Freedman, MD PhD
  – Munir M. Zaman, MD
  – Joanne Brown, MS

• Infant Biorepository and Fatty Acid Analyses
  – Debra DaSilva, RN
  – Clementina DiMonda, RN

• Hyperoxia Lung Model & Terminal Fatty Acid Metabolites
  – Calvin Gilkey
  – **Van Dyke Lab (Forsyth Institute)**
    • Thomas Van Dyke, DDS, PhD
    • Alpdogan Kantarci, DDS, PhD
    • Hatice Hasturk, DDS, PhD

• Lipid Emulsions (Preterm Piglet Model)
  – **Burrin Lab (Baylor)**
    » Douglas Burrin, PhD
    » Barbara Stoll, PhD
Thank You

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