What’s in a bag?
A Clinical Review of Parenteral Nutrition
Ibrahim Sammour, MD FAAP

Objectives

• Background
• Indications in the NICU
• Risks and Complications
• What is in the bag?
  – Protein
  – Carbohydrate
  – Fats
  – Others
• Cycling TPN

Background

• Preterm infants:
  – have limited nutrient stores at birth.
  – Take time to establish enteral feeding
  – Are at risk of accumulating significant nutrient deficits
  – Frequently suffer poor growth
  – Are at risk for congenital or acquired gut disorders such as NEC

Poor nutrition can predispose to poor neurodevelopmental outcomes
Intake Requirements

- To prevent CATABOLISM
  - 40 to 50 Kcal/Kg/day is needed
- For growth
  - 90 to 110 Kcal/kg/day
  - 3.5 to 4 g/kg/day of Protein
  - 3 to 4 g/kg/day of fat

Example

- A 450 to 500g 24 week infant
  - 90% water
  - Has around 50 g of dry tissue, most of which is protein
    - Without parenteral nutrition, 1/3 of his total protein can be consumed in a 24 hour period

Indications

- Infants born extremely preterm or with very low birth weight (less than 1500g)
- As a bridge to enteral nutrition
- As a sole source of nutrition
  - Necrotizing Enterocolitis
  - Short Gut Syndrome

- PN avoids negative nitrogen balance
- Promotes weight gain
- Is associated with positive neurocognitive outcomes

Risks and Complications

- Line associated complications
  - Umbilical Venous Lines (UVC)
    - Hepatic thrombosis
  - Peripherally Inserted Central Catheters (PICC)
    - Localized skin infections
    - Thrombophlebitis
    - Invasive bacterial and fungal sepsis
    - Erosion through vessels and structures
      - Pericardial effusions and possible tamponade
      - Pleural effusions
      - Peritoneal ascites
Risks and Complications

- PN solutions are always hypertonic and hyperosmolar
  - “Safe” Peripheral administration 800 to 1,200 mosm/L
  - Infusions of > D12.5 should be through a central line
- Aluminum contamination
  - Worse neurodevelopmental outcomes
  - Worse bone mineralization

- Lipid infusions
  - Short term hypertriglyceridemia
  - Long term ? Possible increase in aortic stiffness
- TPN induced cholestasis and liver injury
  - Can end up in cirrhosis

What’s in the bag?

- Major Nutrients:
  - Carbohydrates
  - Proteins
  - Lipids

- Electrolytes:
  - Sodium
  - Potassium
  - Chloride
  - Calcium
  - Magnesium
  - Phosphate
  - Acetate

What's in the bag?

- Vitamins
- Trace minerals
  - Chromium
  - Copper
  - Levocarnitine
  - Selenium
  - Manganese
  - Zinc

- Carbohydrates
  - Dextrose
    - May need to be limited in preterm and sick neonates because of hyperglycemia
    - Decreasing Glucose Infusion Rate (GIR) to a minimum of 4mg/kg/min
  - Hyperglycemia
    - Increased mortality
    - Intraventricular hemorrhage
    - Sepsis
    - Chronic lung disease
• Provision of proteins as amino acids is associated with lower glucose levels
  – Possible stimulation of the Insulin/IGF-1 axis

• VLBW at risk for Negative Nitrogen Balance
  – Protein loss of 0.5-1g/kg/day without AA supplementation.

• Undernutrition
  – Irreversible deficits in brain growth
  – Abnormal Neurodevelopment

What kind of Amino Acids do we have?
So why TrophAmine?

Cysteine HCl?

- A conditionally essential amino acid
- Use in TPN:
  - Increases Calcium and Phosphorus solubility in solution

"Aggressive PN"

- Starting relatively high dose Amino acids (2-3) g/kg/day as PN within hours of birth
  - Reduce the incidence and severity of ex-utero growth retardation

Aggressive Early Total Parenteral Nutrition in Low-Birth-Weight Infants

- Early TPN:
  - Protein/Amino Acids of 3.5 g/kg/day
  - Intralipid 3g/kg/day
  - Within 2 Hours of birth

- Late TPN:
  - Dextrose 5-10% for the first 48 hours
  - Protein/Amino Acids of 2 g/kg/day and intralipid 0.5 g/kg/day after 48 hours and advanced per study protocol
**Lipids**

- **Benefits:**
  - High caloric density
  - Safe to start early on day of life

- **Prerequisites for a lipid emulsion:**
  - Provide essential fatty acids
  - Maintain long-chain polyunsaturated fatty acid (PUFA) levels
  - Reduce lipid peroxidation

- **Key Omega Fatty Acids:**
  - \( \omega-6 \) Linoleic
  - \( \omega-3 \) Lenolenic

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### Table 1: Neonatal Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>ETPN (n = 16)</th>
<th>LTPN (n = 16)</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>27.3 ± 1.6</td>
<td>26.8 ± 1.5</td>
<td>0.65</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>996 ± 261</td>
<td>948 ± 234</td>
<td>0.25</td>
</tr>
<tr>
<td>5-minute Apgar score</td>
<td>7 (3 to 8)</td>
<td>6 (3 to 8)</td>
<td>0.78</td>
</tr>
<tr>
<td>Gender (male : female)</td>
<td>10/6</td>
<td>9/7</td>
<td>0.76</td>
</tr>
<tr>
<td>Oxygen Index</td>
<td>48.8 ± 0.7</td>
<td>47.2 ± 0.8</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Mean ± SD.
Median (range).

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### Table 2: Laboratory Values

<table>
<thead>
<tr>
<th></th>
<th>ETPN</th>
<th>LTPN</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>7.7 ± 0.4</td>
<td>6.2 ± 0.4</td>
<td>0.02*</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>83.0 ± 5.5</td>
<td>92.8 ± 6.1</td>
<td>0.26</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>70.9 ± 5.8</td>
<td>84.9 ± 10.1</td>
<td>0.31</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>28.1 ± 0.5</td>
<td>33.9 ± 0.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9 ± 0.06</td>
<td>1.0 ± 0.09</td>
<td>0.47</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>83.8 ± 5.2</td>
<td>101.1 ± 5.4</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

Values presented as mean ± SD.

*Denotes statistical significance.

### Table 3: Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>LTPN (n = 15)</th>
<th>ETPN (n = 14)</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD</td>
<td>8</td>
<td>9</td>
<td>0.71</td>
</tr>
<tr>
<td>Sepsis</td>
<td>7</td>
<td>6</td>
<td>0.73</td>
</tr>
<tr>
<td>IHI</td>
<td>5</td>
<td>4</td>
<td>0.45</td>
</tr>
<tr>
<td>PDA</td>
<td>7</td>
<td>7</td>
<td>1.00</td>
</tr>
<tr>
<td>ROP</td>
<td>3</td>
<td>2</td>
<td>0.74</td>
</tr>
</tbody>
</table>

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**Lipid Sources**

- **Soybean Oil**
  - Pros: Omega-6, linoleic acid
  - Cons: Metabolites may be toxic and can induce inflammatory cytokines

- **Coconut Oil**
  - Pros: Rich in medium-chain triglycerides
  - Cons: None

- **Olive Oil**
  - Pros: Rich in Oleic acid and \( \alpha \)-tocopherol (anti-oxidant)

- **Fish Oil**
  - Pros: Long chain Omega-3 fatty acids (EPA, DHA)

**Intralipid**
**ClinOleic**
**SMOF Lipid**
**Omegaven**

Images Courtesy of Medscape
Safety and Efficacy of Early Parenteral Lipid and High-Dose Amino Acid Administration to Very Low Birth Weight Infants

Hector Kanters-Bruck, MD, PhD, * Marjolein Van Der Horst, MD, PhD, + Zonia J. Baker, MD, PhD, * Chico H. P. van den Akker, MD, PhD, + Kloofen-Diest, * Josine L. Beetsma, * Antoo Vermeulen, PhD (D), + Henk Schenkein, PhD, ** and Johannes B. van Goudoever, MD, PhD ***

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Inclusion Criteria

• Gestational Age ≤ 28 weeks
• Received multidisciplinary consultation at 1 year.
  – Measured developmental quotient (DQ) at 1 year
    • One Center
    • Over a 2 year period

Better Nitrogen Balance in R groups

Day 2


Perinatal characteristics of the population studied.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of the mother (years)†</td>
<td>32.3 ± 5</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>9 (19%)</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>41 (86%)</td>
</tr>
<tr>
<td>Inborn</td>
<td>39 (81%)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>26.8 ± 1</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>27 (58%)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>928 ± 197</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>35.2 ± 2.6</td>
</tr>
<tr>
<td>Birth head circumference (cm)</td>
<td>24.4 ± 1.4</td>
</tr>
<tr>
<td>Intra-uterine growth retardation</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Hyaline membrane disease</td>
<td>37 (77%)</td>
</tr>
<tr>
<td>Persistent ductus arteriosus</td>
<td>23 (48%)</td>
</tr>
<tr>
<td>Intra-ventricular hemorrhage ≥ grade 2</td>
<td>20 (42%)</td>
</tr>
</tbody>
</table>

* mean ± Standard Deviation (SD) or n [%].

Assessed for eligibility (n = 419)

Exclusion criteria (n = 121)
• No informed consent (n = 121)
• No opportunity to obtain consent (n = 121)
• Child not treatment (n = 121)
• Language barrier (n = 121)
Carnitines

- Synthesized in the body from Amino acids and are conditionally essential nutrients
- Functions:
  - Energy: Transport of fatty acids into the mitochondria
  - Immune modulation
- Excess: Excreted through the kidneys
- Deficiency: Progressive cardiomyopathy, encephalopathy and skeletal myopathy

Chromium

- Functions:
  - Possible role in insulin signaling
- Excess: Can lead to rampant oxidation when ingested; hemolysis, renal and liver failure
- Deficiency:
  - Possible impaired glucose tolerance
  - Possible weight loss

Copper

- Functions:
  - Oxygen processing: Cytochrome C oxidase, superoxide dismutase (SOD)
- Excess: Deposits in liver and the brain (Wilson’s disease)
- Deficiency: Anemia, neutropenia, impaired growth

Manganese

- Function:
  - Antioxidant: component of superoxide dismutase (SOD)
  - Cofactor in oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases, lectins and integrins
- Excess: Deposits in the basal ganglia in the brain and can lead to parkinson like features in adults (Manganism) and decreased IQ scores in children.
- Deficiency: Skeletal deformation and poor wound healing
Selenium

- Function:
  - Anti-oxidant: Cofactor for glutathione peroxidases and thioredoxin reductase
  - Thyroid: Cofactor for deiodinases that activate/deactivate T4/T3
- Excess: Toxic (Selenosis)
- Deficiency: Dilated cardiomyopathy (Keshan disease in China)

Zinc

- Functions:
  - Appears in all classes of enzymes
    - Structural: Zinc fingers
    - Functional: DNA Transcription
  - Excess: Impairs Copper absorption from the gut
  - Deficiency: Poor growth, diarrhea, alopecia, dermatitis, altered cognition and immune function.

Practical Issues

<table>
<thead>
<tr>
<th>Day of Life</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g/kg/day)</td>
<td>Starter 3.4% or 3 if regular TPN</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Lipids (g/kg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1500g</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&gt;1500g</td>
<td>0-1</td>
<td>1-2</td>
<td>2-3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cysteine (mg/kg of protein)</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>

Hyperglycemia

- Adjusting Dextrose:
  - Persistent hyperglycemia (120-200 mg/dL) AND glucosuria
  - Persistent hyperglycemia > 200 mg/dL
- Dextrose should not be dropped below 5% (GIR 4mg/kg/min)
- Fat calories should not exceed 60% of total

Gram Negative Sepsis

- Association between lipid use and worse outcomes with gram negative sepsis historically reported
  - Reducing IL to 1g/kg/day
Cholestasis or Liver Disorders

- Requires adjusting:
  - Manganese (50% reduction or twice weekly)
  - Copper (50% reduction or twice weekly)
  - Intralipids
    - 3 times a week at 1g/kg/day

Prolonged TPN use

- “Cycling” should start after 2 weeks
- Reduction of Manganese and copper in TPN after 2 weeks

Renal Dysfunction

- Requires adjusting:
  - Selenium
  - Possible need to reduce Amino acids

TPN Cycling

- Lipogenic state: Fatty Liver
  - Serum FA levels drop
- Peripheral utilization of Amino acids in skeletal muscles

Cyclic Hyperalimentation: An Optimal Technique for Preservation of Visceral Protein

B. MAINI, M.D., G. L. BLACKBURN, M.D., Ph.D.,
B. R. BISTRIAN, M.D., M.P.H., Ph.D., J. P. FLATT, Ph.D.,
J. G. PAGE, M.B., Ch.B., F.R.C.S., A. BOTHE, M.D.,
P. BENOTTI, M.D., AND H. Y. RIENHOFF, B.A.
Division of Surgery, Boston City Hospital,
Boston University School of Medicine; Sears Surgical Laboratory;
Cancer Research Institute, New England Deaconess Hospital;
Harvard Medical School, Boston, Massachusetts 02215

Submitted for publication December 22, 1975

Journal Of Surgical Research 20, 515-525 (1976)
So How to Cycle?

Summary

- Early and “aggressive” PN/IL use
  - Associated with better nitrogen balance and improved neurologic outcomes
  - Is well tolerated with minimal side effects
- Care must be taken in managing trace minerals as excess or deficiency may be harmful
- Cycling of TPN helps reduce liver injury and cholestasis

Alternative
References