Controversies in Parenteral Nutrition

Christopher Duggan, MD, MPH
Center for Nutrition
Center for Advanced Intestinal Rehabilitation (CAIR)
Division of Gastroenterology, Hepatology and Nutrition
Boston Children’s Hospital
Harvard Medical School
Boston, MA

DISCLOSURE

In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

Learning Objectives

• To review indications for intravenous fat emulsions in patients with intestinal failure
• To review strategies for parenteral micronutrient supplementation in the setting of manufacturing shortages
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LONG-TERM PARENTERAL NUTRITIONAL SUPPORT AND INTESTINAL ADAPTATION IN CHILDREN WITH SHORT BOWEL SYNDROME: A 25-YEAR EXPERIENCE
Rudolph E. Quan-Twinn, MD, Markus A. Arndt, MD, Louis Bending, RN, Anna Haskelson, RN, Michelle Marquardt, MD,
Nancy Charles Simonas, MD, and Joyce M. Vincent, MD

- 78 patients with
  - PN dependence for > 3 months
  - SBS defined as ≤ 75 cm residual small bowel
- 57/78 (73%) alive median age 9 years
  - Median follow-up: 9 years
  - Range of follow-up: 2.1 – 23 years

Correlation of survival with cholestasis

Among the 168 infants with sufficient data to assess for the presence of cholestasis at baseline, 125 children had cholestasis, and their cumulative percentage of survival was significantly lower than in the 43 without cholestasis (79% vs 95% at 1 year, and 73% vs 88% at 3 years; \( P = .03 \)).

**Birthweight and PNALD**

![Chart showing the relationship between birthweight and PNALD](chart)

**FIGURE 6A:** Relationship between the incidence of parenteral nutrition-associated liver disease (PNALD) and low birth weight. Adapted from Batta EY et al.\(^7\)

![Chart showing the effect of age at first infection on the development and severity of parenteral nutrition-associated cholestasis in infants with intestinal resection. Adapted from Landgren JM, Antonius R, Callegaro S, Schiller MED. Infection and cholestasis in infants with intestinal resection and long-term parenteral nutrition. J Pediatr Gastroenterol Nutr. 2000;30(1):11-7.](chart)
### Protein intake

<table>
<thead>
<tr>
<th>Variable</th>
<th>2.5 g/kg/d</th>
<th>4.0 g/kg/d</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct bili &gt; 2 mg/dL</td>
<td>27%</td>
<td>33%</td>
<td>NS</td>
</tr>
<tr>
<td>Days of PN before cholestasis</td>
<td>47 +/- 6</td>
<td>27 +/- 4</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Peak direct bili</td>
<td>3.2 +/- 0.3</td>
<td>8.4 +/- 1.6</td>
<td>.001</td>
</tr>
</tbody>
</table>

Vileisis, RA et al., J Pediatr 1980; 96:893-897

### PN-associated liver disease

- Nutrient deficiency
  - Taurine
  - Choline
  - EFA
  - Vitamin E
  - Zinc

- PN toxicity
  - Energy
  - Protein
  - Individual amino acids
  - Fats

### Risk Factors for Parenteral Nutrition–associated Liver Disease Following Surgical Therapy for Necrotizing Enterocolitis

- Cohort study of 464 infants with NEC
- Enrolled across 6 centers
- 2004 – 2007

Duro et al., JPGN 2011
TABLE 1. Independent predictors of PNAID (N = 127)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks of PN*</td>
<td>2.37</td>
<td>(1.56 - 3.60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Small bowel repair</td>
<td>4.98</td>
<td>(1.97 - 12.51)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

CI = confidence interval; PN = parenteral nutrition; PNAID = parenteral nutrition-associated liver disease.

*Cumulative exposure from birth through 4 weeks after surgery.
Gura et al.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Comparison of lipid emulsions (10g fat/100mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>Intralipid® (Barré Healthcare/Presencia S.A.)</td>
</tr>
<tr>
<td>Oil source</td>
<td></td>
</tr>
<tr>
<td>Soybean</td>
<td>10</td>
</tr>
<tr>
<td>Sunflower</td>
<td>0</td>
</tr>
<tr>
<td>Fish</td>
<td>0</td>
</tr>
<tr>
<td>1-Eno:</td>
<td></td>
</tr>
<tr>
<td>Linolic</td>
<td>50</td>
</tr>
<tr>
<td>e-Linolenic</td>
<td>5</td>
</tr>
<tr>
<td>DHA</td>
<td>0</td>
</tr>
<tr>
<td>EPA</td>
<td>0</td>
</tr>
<tr>
<td>Docos</td>
<td>26</td>
</tr>
<tr>
<td>Palmitic</td>
<td>10</td>
</tr>
<tr>
<td>Stearic</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Dihomo- 
alpha-linolenic acid, DHA: docosahexaenoic acid

Experience with Omega 3 fatty acids

Gura K et al., Pediatrics 2006; 118:197-201

Safety and Efficacy of a Fish-Oil-Based Fat Emulsion in the Treatment of Parenteral Nutrition–Associated Liver Disease

- 18 infants with SBS who developed cholestasis were
  - Taken off IL
  - Placed on Omegaven (1 g/kg/d)
- Historical cohort of 21 infants followed at same institution

Pediatrics 2008; 121:e678
Direct bilirubin trends

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Fish-Oil (N = 117)</th>
<th>After Fish-Oil (N = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>10.3 (5.1)</td>
<td>10.2 (5.6)</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dL)</td>
<td>6.4 (3.0)</td>
<td>6.1 (3.2)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.8 (0.4)</td>
<td>0.8 (0.4)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>93 (69)</td>
<td>94 (71)</td>
</tr>
<tr>
<td>Hypothyroidism (triglycerides &gt; 400 mg/dL)</td>
<td>12 (9)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>10.9 (9.9)</td>
<td>10.9 (9.9)</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>0.2 (0.1)</td>
<td>0.2 (0.1)</td>
</tr>
<tr>
<td>Mean bilirubin (mg/dL)</td>
<td>6.4 (3.0)</td>
<td>6.1 (3.2)</td>
</tr>
</tbody>
</table>

Comparison of Safety Markers for the Period Before Fish-Oil, From 30 Days After Starting Fish-Oil Until the End of Follow-up (Primary Comparison) and From the Date on Which Fish-Oil Was Started Until Day 30 of Treatment.

Pediatrics 2008; 121:e678
Unanswered questions

• Are these “Omegaven” or “absence of Intralipid” effects?
• What is the natural history of infants treated with omegaven?
• Does improvement of cholestasis herald prevention of cirrhosis?
• Can PNALD be prevented with omega-3 fats?
• Mechanisms?

Intravenous Fat Emulsions Reduction for Patients with Parenteral Nutrition–Associated Liver Disease

J Pediatrics 2011

Controversies

• Is it safe to provide so many calories using parenteral dextrose?
  – Dalton et al., NASPGHAN 2013
• Is it effective to limit fat to 1 g/kg/d re: cholestasis prevention?
  – Nehra et al., JPEN 2013
  – Levit et al., PAS 2013
61 infants with surgical GI disease who received PN for at least 3 weeks at BCH

- 29 received 1 g/kg/d of IL
- 32 received 2-3 g/kg/d
“Our” Current Approach

- Limit IL dose to 1 g/kg/day among all patients likely to be on PN for > 3 weeks
  - NAC
  - Including NICU
  - Make up calories with dextrose
- If a patient meets criteria for Omegaven protocol, switch them to 1 g/kg/day of this experimental therapy

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“Total” parenteral nutrition

Prevalence of micronutrient deficiencies during PN weaning

Prevalence of micronutrient deficiencies during full EN

Yang et al., J Pediatr 2011
Parenteral component shortages

- Phosphate
- Multivitamins
- Trace elements
- Ethanol


3 premature infants in NICU with cholestasis and PN dependency developed skin lesions
- Blood, urine, CSF and wound cultures were negative
Parenteral Component Shortages

- Raw material shortages
- Discontinuations
- Fewer manufacturing firms
- Limited capacity of remaining companies to increase supplies
SBAR: 4/24/2013 Medication Backorders
S Sodium Phosphate and Potassium Phosphate are on national backorder at this time.
B These products are used in parenteral nutrition, hypophosphatemia, and in diabetic ketoacidosis IV fluids. These electrolytes have been on backorder with small allocations for a period of time and supply is now almost depleted.
A 1. Sodium Phosphate 3 mmol/mL injection – 3 vials remaining
   2. Potassium Phosphate 3 mmol/mL injection – 5 vials remaining
R Effective immediately – 4/24/2013
   · Sodium Phosphate injection – Supply is depleted except for a very small number of vials (3). These vials will be sequestered for ICU emergent use and/or in the DKA patient population. Pharmacy is expecting a shipment by the end of this week.
   · Potassium Phosphate injection – Supply is almost depleted except for a very small number of vials (5). This product will be sequestered for ICU emergent use and/or in the DKA patient population.
   · DKA floorstock fluids as they currently exist will no longer be manufactured by Pharmacy due to this backorder.
   · Phosphate will NOT be included in parenteral nutrition mixtures at this time.

Recommendations for Trace Element Shortages
For patients receiving 7 nights of parenteral nutrition (PN) and/or <50% enteral feeds
Biochemical monitoring: complete blood count (CBC) with differential, copper, ceruloplasmin, CRP, vitamin A*
   *Vitamin A to be checked if not monitored in the past 6 months. Rationale: evaluate for risk of hypervitaminosis A

   Patients 2 years and older:
   · Start Flintstones® Complete multivitamin for supplementation
   Patients under 2 years of age:
   · Provider discussion

For patients receiving less than 7 nights of PN and >=50% enteral feeds:
Biochemical monitoring: CBC with differential, copper, ceruloplasmin, CRP at time patient is impacted.
   If impacted by zinc or selenium shortage, monitor these levels
   No additional supplementation needed. Encourage copper (zinc if applicable) rich foods (see appendix)
   Repeat CBC with differential, copper, ceruloplasmin (zinc and selenium as applies) in 2 months’ time

   Courtesy Home PN Program Boston Children’s Hospital
Conclusions

- Current approach to prevent/treat PNALD is not 100% clear at this time.
- Shortages of components of PN have significant implications for our patients.
- Biochemical monitoring is critical to document nutrient deficiency states.
- Advocacy efforts must continue.