2014 Update on TPN-associated Cholestasis
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Disclosures
In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or providers of commercial services discussed in this CME activity.

Learning objectives
1. Identify clinical signs, lab measurements, and patient-specific risk factors that will help achieve timely diagnosis of TPN-associated cholestasis.
2. Gain exposure to various treatment algorithms such as proactive lipid minimization strategies for TPN-associated cholestasis.
3. Discuss and debate with colleagues your own opinions regarding novel lipid formulations and treatments for TPN-associated cholestasis.

TPN-associated cholestasis: Risk factors
- Precise etiology remains unknown
- Risk factors are well-characterized:
  - Prematurity
  - Lack of enteral feeds
  - Intestinal surgery
  - Repeated bouts of sepsis
  - Lipid loads

Histology and urgency for timely diagnosis
- Life-threatening, especially in premature infants
- Can progress to ESLD and cirrhosis/need for OLT

Cholestasis (eventually) resolves when off PN/IL

Sources:
TPN-associated cholestasis and outcomes

High Rates of Mortality and Morbidity Occur in Infants With Parenteral Nutrition–Associated Cholestasis

Theresa C. Willis, MD; Beth A. Carter, MD; Stefanie P. Rogers, MD; Keli M. Hawthorne, MS; Ponni D. Hicks, PhD; and Steven A. Ahearn, MD

TPNAC—Typical clinical findings

- Persistent Jaundice
- Hepatomegaly (occurs within 2-4 weeks)—Increased AST, ALT, bilirubin
- Portal Hypertension:
  - Splenomegaly
  - Portal Hypertension: 
    - Collapsed mesenteric veins
  - GI bleeding:
    - Low Hct, high PT on labs
  - Other:
    - Ostomies
    - Poor po advancement

Composition of parenteral fat emulsions

<table>
<thead>
<tr>
<th>Oil</th>
<th>Intralipid®</th>
<th>Omegaven®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean (ω6 FA)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fish (ω3 FA)</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Fat

- Linoleic: ++++ +
- Linolenic: ++++ +
- EPA: No Yes
- DHA: No Yes

Other

- Phytosterols: Yes No

Omega 3 FA emulsions for TPN-associated liver disease

- 2006: Gura et al. (Boston) report reversal of IF-associated liver disease in 2 infants after Omega 3 FA emulsion (Omegaven®). (Pediatrics)

Controversial issues regarding Omegaven® studies and lipid emulsions

- "These infants must become EFA-deficient."  False
- "These infants must not grow well!"  False
- "Early studies used historical controls for comparison of unnecessary lipid loads."  True
- "If the lipid used or the lipid type?"  Both
- "Some Omegaven® recipients will require transplant, die or have continued LD."  True

Conclusions:

- Younger gestational age infants had higher degrees of cholestasis, longer resolution times, and increased mortality.
- Higher cholestasis—longer resolution time
- 10/57 (17.5 %) infants died.
- Fish oil-derived lipid emulsion led to resolution of cholestasis in all surviving infants.
Phytosterols are components of soy-derived Intralipid®

<table>
<thead>
<tr>
<th>STEROLS</th>
<th>Content in 20% IL/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total phytosterols</td>
<td>740 mg</td>
</tr>
<tr>
<td>β-sitosterol</td>
<td>410 mg</td>
</tr>
<tr>
<td>Campesterol</td>
<td>168 mg</td>
</tr>
<tr>
<td>Stigmasterol</td>
<td>152 mg</td>
</tr>
</tbody>
</table>

BSEP (Bile Salt Export Pump) is involved in bile acid (BA) homeostasis

Hypothesis-Phytosterols and TPN-Associated LD

Stigmasterol, a phytosterol present in soy-derived lipid infusates, antagonizes BA-activated FXR target genes involved in BA homeostasis (e.g. BSEP)

**Methods: Quantitative RTPCR**

**DAY 0:**
- HepG2 (Liver) cells grown to 75% confluency
- Treatments (X 24 hrs):
  - Vehicle
  - CDCA, a bile acid (100 mM)
  - StigAc, a phytosterol (10 mM)
  - CDCA (100 mM) + StigAc (10 mM)

**DAY 1:**
- Harvest cells
- RNA purification
- qRTPCR for FXR target gene, BSEP, compared to 18s control

Lipid Loads and TPN-associated Liver Disease


- **TCH Intestinal Rehabilitation Clinic lipid strategies:**

  1. Entry into our IRB-approved Omegaven® protocol if criteria met (B Con ≥ 4 or B Con ≥ 2 if extreme short-bowel syndrome) or

  2. Limit soy-derived lipid load to 1 gm/kg/day or less (depending on amount of enteral feeds and predicted PN duration).
**Strategy: lipid minimization protocol**

NICU pts at University of Michigan Mott’s Children’s Hospital

**Entry criteria:** at least 2 weeks IV PN with soy-derived lipid emulsion typically at 3 gm/kg/day; serum D bilir > 2.5 mg/dl or T bilir >5 (n=31)

Lipid Minimization Group: Soy-derived lipid 1 gm/kg/d twice weekly; no other lipid

Historical controls: Soy-derived lipids between Aug 2003 and July 2005; similar bilir, gestation age, primary dx, and birthweight to fat restriction group.

**Results: Lipid minimization protocol**

**Preliminary results:**

• Lipid minimization group had statistically significant Total bilirubin reduction vs Control

• No detrimental effects on growth in lipid minimization group

• No irreversible essential fatty acid deficiency (EFAD) in lipid minimization group.

8 infants in the lipid restriction group developed mild EFAD, which was reversible after increase of lipid load to 1 gm/kg/d three times weekly, or, if necessary, 2 gm/kg three times weekly.

**Strategy: Cycling parenteral nutrition**

**Proposed benefits:**

• Theoretical decreased risk of cholestatic liver disease

• 2-6 hour cycle off PN promotes GI hormones

• Improved quality of life at home

**Caution:**

• No prospective, randomized controlled trials confirming the hepatoprotective effect of PN cycling

• Monitor for hypoglycemia during cycles off PN in patients with end-stage liver disease

**Reality:**

• With novel formulations of lipids and minimization of lipid loads, end-stage liver disease associated with PN is becoming much less common, and cycling PN much easier/safer to implement

**Strategy: Ethanol locks to central lines**

• Ethanol-containing solution in catheter lumen and allowed to remain in place for a certain period of time

• Bactericidal and fungicidal via denaturing of cell membranes

• Monitor for hypoglycemia, arrhythmias, local venous irritation, and flushing

• Effective alone or in combination with other agents for eradication of various microorganisms

• Studies have suggested use of ≥50% ethanol solutions (TCH IRB-approved protocol uses 70% Ethanol)
Ethanol locks in pediatric TPN

- Retrospective study of children with short bowel syndrome receiving home PN through CVCs
- Daily 70% ethanol lock for 4-14 hours
- 10 patients with 26 CVCs over 3556 catheter-days
- In 5 patients before ethanol lock therapy, CRBSI rate was 11.15/1000 catheter-days; after ethanol lock therapy the rate was 2.06/1000 catheter days
- In 5 patients with no ethanol lock-free period, CRBSI rate was 1.85/1000 catheter-days
- No adverse reactions due to ethanol use were reported


Ethanol lock strategy: Helpful hints

- Some literature suggests that polyurethane based CL do not withstand ethanol exposure as well as silicone-based
- Guidelines for indwell volumes are available in the literature (Arch Pediatr Adolesc Med/ Jul 18, 2006)
- Pediatric surgeons may cut length of CL to accommodate small infants, so published ethanol indwell volumes may not apply to all
  - Consider determining indwell volume of lumen by infusing 0.5-1.4 ml saline into CL and then drawing back volume until “flash” of blood seen.
- TCH Experience: Exposure of heparin to ethanol may facilitate line occlusions.
  - After ethanol solution is withdrawn in preparation for next PN infusion, flush line well with normal saline to clear line of ethanol prior to heparinized PN in line.

Other strategies worthy of mention...

- Max glucose infusion rate at our Intestinal Rehabilitation Center is ~14 mg/kg/min; ideal GIR is ~12 mg/kg/min. (Less risk for hepatic steatosis and bacterial growth).
- Typical caloric needs across all diagnoses at our Center is 100-125 kcal/kg/day max
  - Avoid the urge to overfeed parenteraly!!
- Currently, there are many injectable electrolytes and minerals that are on backorder or shortage (e.g. Calcium Gluconate, K acetate, K phos)
  - Helpful alternative strategies at ASPEN website: http://www.nutritioncare.org/News/Product_Shortages/Parenteral_Nutrition_Components_of_Shortages_Update/
  - Consider notifying the FDA about the extent and consequences of such shortages. This may help effect action to get needed PN components for your patients

Summary

- TPN-associated liver disease can carry significant morbidity and mortality if left untreated/unmanaged.
- Strategies to avert TPN-associated liver disease include:
  - Omega-3 FA based intravenous lipids - safe, not associated with EFAD, favorable growth, due to date, not compared head-to-head via randomized controlled trials vs any derived emulsions.
  - Soy derived lipid minimization strategies - various lipid minimization strategies were described. We actively implement lipid minimization in any infant over 2 months of age who is predicted to be on PN X 2+ months.
  - Ethanol lock therapy - in effort to avert CL infections in patients with IF. This practice has been used for years and has long-term benefits in reducing sepsis-associated cholestasis and preservation of central access sites.

Type of Catheter

<table>
<thead>
<tr>
<th>Single lumen tunneled catheter</th>
<th>Double lumen tunneled catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Volume</td>
<td>Dose Volume</td>
</tr>
<tr>
<td>Broviac 4.2 Fr (ID 0.7 mm)</td>
<td>Med-comp Catheter</td>
</tr>
<tr>
<td>0.8 ml</td>
<td>1.2 ml</td>
</tr>
<tr>
<td>Broviac 6.6 Fr (ID 1 mm)</td>
<td>Hickman Double Lumen</td>
</tr>
<tr>
<td>0.8 ml</td>
<td>7 Fr Distal (red) (ID 1 mm)</td>
</tr>
<tr>
<td>1.2 ml</td>
<td>1.2 ml</td>
</tr>
<tr>
<td>Med-comp Catheter</td>
<td>Hickman Double Lumen</td>
</tr>
<tr>
<td>1.2 ml</td>
<td>9 Fr Proximal (white) (ID 0.7 mm)</td>
</tr>
<tr>
<td>1.2 ml</td>
<td>1.2 ml</td>
</tr>
<tr>
<td>Type of Port-a-cath</td>
<td>Type of Port-a-cath</td>
</tr>
<tr>
<td>Any port</td>
<td>1.4 ml</td>
</tr>
</tbody>
</table>

Ethanol lock volume guidelines

bac@bcm.edu
Video would be placed here, as would still images.