


2014 Update on TPN-associated Cholestasis

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Pediatrics



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


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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.


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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

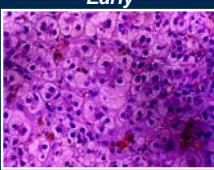
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Histology and urgency for timely diagnosis

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

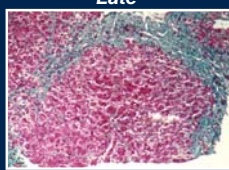
Early



Cholestasis, ballooning of hepatocytes

→


Late



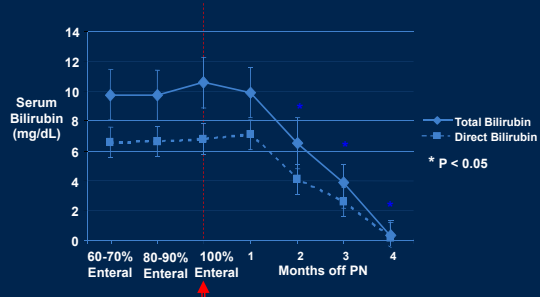
Biliary cirrhosis- associated with death within 6 months of onset

Refs: 1. Carter BA and Shulman RJ, *NCPGastroHep*, May 2007
2. Kelly DA, *Nutrition*, 1998


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Cholestasis (eventually) resolves when off PN/IL



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TCH: TPN-associated cholestasis and outcomes

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

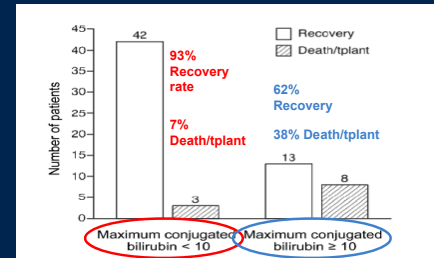
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TPN-associated cholestasis and outcomes



Willis TC et al, JPEN, 2009

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TPNAC—Typical clinical findings

- **Persistent Jaundice**
- **Hepatomegaly** (occurs within 2-4 weeks)—Elevated AST, ALT, bili. Serum Bas rise first.
- **Portal Hypertension:**
 - Splenomegaly & ↓ Platelets
 - Ascites
 - Caput medusae
 - GI Bleeding
 - Low WBC, Hgb, Plt on labs indicator of portal HTN (but don't wait for this to happen before therapeutic intervention!)
- **Ostomies**
- **Poor po advancement**



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Composition of parenteral fat emulsions

	Intralipid®	Omegaven®
Oil		
Soybean (ω6 FA)	Yes	No
Fish (ω3 FA)	No	Yes
Fat		
Linoleic	+++++	+
Linolenic	++++	+
EPA	No	Yes
DHA	No	Yes
Other		
Phytosterols	Yes	No

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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)
- **2008, 2009:** Same group from Boston report use of Omega 3 FA lipid emulsion for IF-associated LD in larger cohorts (n=18; n=42) (Pediatrics & Ann Surgery)

Controversial issues regarding Omegaven® studies and lipid emulsions

↓	↓	↓	↓	↓
"These infants must become EFA-deficient"	"These infants must not grow well"	"Early studies used historical controls for comparison → unequal lipid loads"	"Is it the lipid load or the lipid type?"	"Some Omegaven® recipients still require transplant, die or have continued LD."
False^{1,2}	False^{1,2}	True³ → www.clinicaltrials.gov/NCT00512629 "COMPLETED" "No results posted"	Both³	True^{4,5}

1. De Meijer, et al. JPEN, 2010
2. Whitfield, et al. NASPGHAN abstract 2009
3. Carter, et al. Peds Research, 2007
4. Diamond et al. JPEN 2009
5. Soden et al. J Pediatr 2009
6. Premkumar, et al. J Pediatr, 2012. ClinicalTrials.gov NCT00728101

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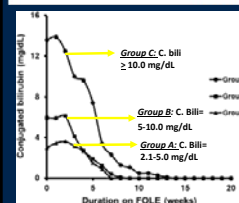


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ORIGINAL ARTICLES

High Rates of Resolution of Cholestasis in Parenteral Nutrition-Associated Liver Disease with Fish Oil-Based Lipid Emulsion Monotherapy

Muralidhar H. Premkumar, MBBS, MRCPCH¹, Beth A. Carter, MD², Keli M. Hawthorne, MS, RD³, Kristi King, MPH, RD⁴, and Steven A. Abrams, MD¹



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.

ClinicalTrials.gov: NCT00738101

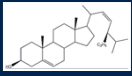
Pediatrics



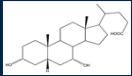
Phytosterols are components of soy-derived Intralipid®



20% Intralipid®
(soy-derived)



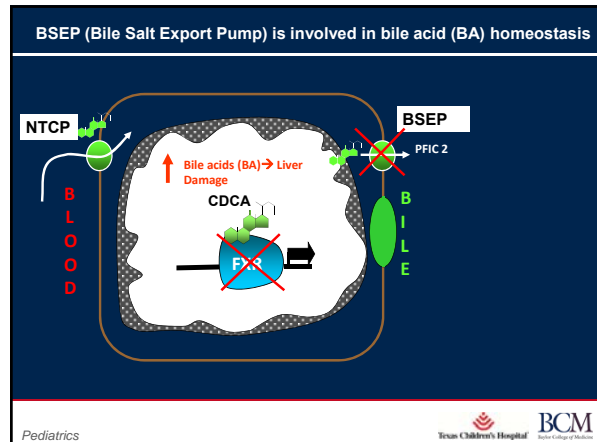
Stigmasterol



Chenodeoxycholic acid
(CDCA-human bile acid)

STEROLS	Content in 20% IL /L
Total phytosterols	740 mg
β-sitosterol	410 mg
Campesterol	168 mg
Stigmasterol	152 mg

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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)

↓

Decreased ability of hepatocytes to unload toxic bile acids via BSEP (Bile Salt Export Pump) → liver damage and cholestasis

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Methods : Quantitative RTPCR

DAY 0:

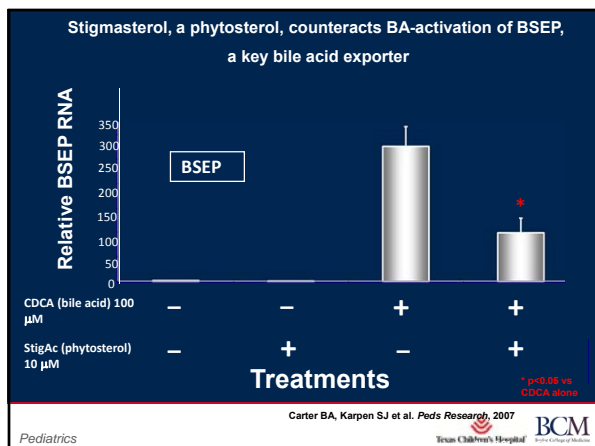
- HepG2 (Liver) cells grown to 75% confluency
- Treatments (X 24 hrs):**
 - Vehicle
 - CDCA, a bile acid (100 mM)
 - StigAc, a phytosterol (10 mM)
 - CDCA (100 mM) + StigAc (10 mM)

DAY 1:

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

Carter BA, Karpen SJ et al. *Peds Research*, 2007

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Lipid Loads and TPN-associated Liver Disease

- Lipid reduction strategy to reduce IF-associated cholestasis was first described in 1982. (Allardyca, *Surg Gynec Obstet*. Additional investigations regarding the relationship between lipid loads and liver disease followed (Cavlicchi et al. *Transp Proc* 1998 & Colomb V et al. *JPEN* 2000).
- TCH Intestinal Rehabilitation Clinic lipid strategies:**
 - Entry into our IRB-approved Omegaven® protocol if criteria met (B Conj ≥ 4 or B Conj ≥ 2 if extreme short-bowel syndrome) **or**
 - Limit soy-derived lipid load to 1 gm/kg/day or less (depending on amount of enteral feeds and predicted PN duration).

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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 bili \geq 2.5 mg/dl or T bili $>$ 5 (n=31)

n=14 n=14

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 bills, gestational age, primary dx, and birthweight to fat restriction group.

Cober MP and Teitelbaum DH. *Curr Opin Organ Transplant* 15:330-333, 2010



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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/day three times weekly, or, if necessary, 2 gm/kg three times weekly.

Cober MP and Teitelbaum DH. *Curr Opin Organ Transplant* 15:330-333, 2010

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Novel intravenous lipid emulsion for TPN-associated cholestasis

Is this the "happy medium"?
 ω 6/ ω 3 fatty acids=2.5

S M O F
(SMOFlipid 20%, Fresenius Kabi)

30% 30% 25% 15%

Soybean Oil

- High EFA content (ω 6 predominant)
- +phytosterol
- High PUFAs
- Low α -tocopherol

Medium-chain triglycerides



- Rapidly oxidized for energy provision
- Safe in neonates, long-term administration

Olive Oil

- High monounsaturated Fats (MUFAs)
- Allows reduction of PUFAs
- Low ω 3

Fish Oil

- High (ω 3) anti-inflammatory
- No phytosterols
- Low EFA content

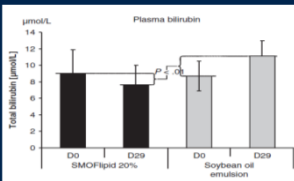
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Original Communication

A New Intravenous Fat Emulsion Containing Soybean Oil, Medium-Chain Triglycerides, Olive Oil, and Fish Oil: A Single-Center, Double-Blind Randomized Study on Efficacy and Safety in Pediatric Patients Receiving Home Parenteral Nutrition



Olivier Coulet, MD, PhD¹; Helena Antebi, MD, PhD²; Claude Wolf, PhD³; Cécile Talbotec, MD⁴; Louis-Gérard Alekandor, MD, PhD²; Odile Corriot, PhD⁴; Michèle Lamor, RN¹; and Virginie Colomb-Jung, MD, PhD¹

Financial disclosure: This study was supported by Fresenius Kabi, Bad Homburg, Germany. **JPN Sept. 2010**





Conclusions:

- SMOFlipid 20% was safe/well tolerated
- Decreased plasma bilirubin in SMOFlipid20% cohort vs. IL cohort
- Increased ω 3 FA and α -tocopherol status in SMOFlipid20% cohort vs. IL cohort without changing lipid peroxidation.

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Strategy: Cycling parenteral nutrition

- Proposed benefits:**
 - Theoretical decreased risk of cholestatic liver disease (Jensen AR et al. *J Ped Surg* 2009)
 - 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

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Strategy: Ethanol locks to central lines

- Ethanol-containing solution in catheter lumen and allowed to remain in place for a certain period of time \rightarrow bactericidal and fungicidal via denaturing of cell membranes
- Benefits include ease of acquisition, low cost, and low likelihood of promoting antibiotic resistance
- Potential adverse effects include CNS depression, arrhythmias, local venous irritation, and flushing
- Effective alone or in combination with other agents for eradication of various microorganisms
- Studies have suggested use of \geq 50% ethanol solutions (TCH IRB-approved protocol uses 70% Ethanol)

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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

Mouw E, et al. *J Ped Surg*. 2008;43:1025-1029.

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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*/Vol 160, Oct 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.

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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 of IF at our Center is 100-125 kcal/day max → Avoid the urge to overfeed parenterally!!
- 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_Component_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

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Thank you!

bac@bcm.edu

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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, but, to date, not compared head-to-head via randomized controlled trials vs soy 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 is safe in our (and other's) hands and has long-term benefits in reducing sepsis-associated cholestasis and preservation of central access sites.

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Ethanol lock volume guidelines

Type of Catheter	Dose Volume
Single lumen tunneled catheter	
Broviac 4.2 Fr (ID 0.7 mm)	0.8 ml
Broviac 6.6 Fr (ID 1 mm)	0.8 ml
Med-comp Catheter	1.2 ml
Type of Catheter	
Double lumen tunneled catheter	
Hickman Double Lumen 7 Fr Distal (red) (ID 1 mm)	1.2 ml
Hickman Double Lumen 9 Fr Proximal (white) (ID 0.7 mm)	1.2 ml
Med-comp 8 or 10 Fr	1.2 ml
Type of Port-a-cath	
Any port	1.4 ml

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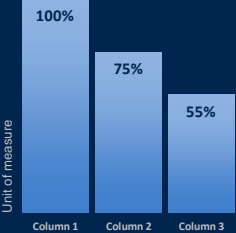
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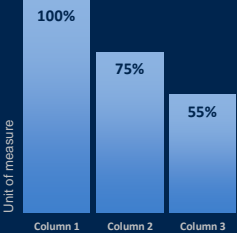



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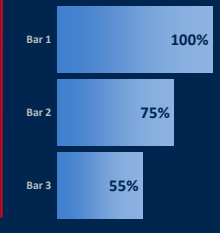



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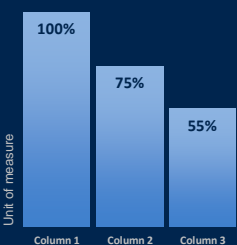



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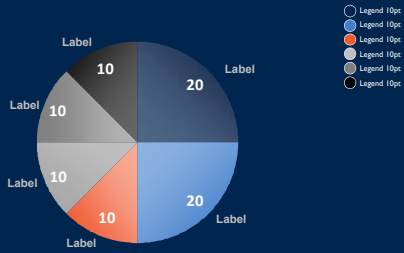


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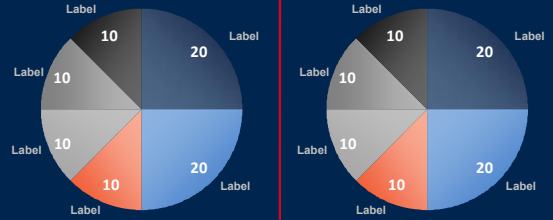
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Video would be placed here, as would still images

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