Long-term complications of TPN

Now that my intestinal failure patients are not dying of liver disease, what else should I worry about?

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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 provider(s) of commercial services discussed in this CME activity.

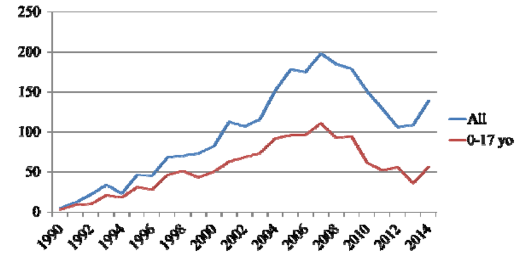
I will briefly mention an intravenous fish oil fat emulsion which is not FDA approved in the United States

Objectives

1. Identify potential complications of lipid minimization strategies
2. Describe an approach to micronutrient monitoring in long term parenteral nutrition
3. Discuss renal and bone complications of parenteral nutrition

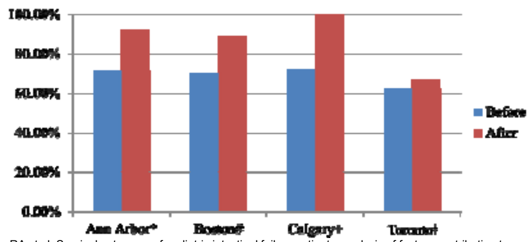
Decrease in number of intestinal transplants -

increase in intestinal rehabilitation programs, decrease in overt liver disease, decrease in sepsis, other aspects of care?



Intestinal Transplants – UNOS data through end 2014
(As of August 1, 2015 – 42 total, 21 children)

Survival before and after establishment of IR team



*Hess RA et al. Survival outcomes of pediatric intestinal failure patients: analysis of factors contributing to improved survival over the past two decades. J Surg Res. 2011;170:27-31
#Modi BP et al. Improved survival in a multidisciplinary short bowel program. J Pediatr Surg 2008;43:20-24
+Sigalet D et al. Improved outcomes in paediatric intestinal failure with aggressive prevention of liver disease. Eur J Pediatr Surg. 2009;19:348-353
‡Diamond IR et al. Neonatal short bowel syndrome outcomes after the establishment of the first Canadian multidisciplinary intestinal rehabilitation program: preliminary experience. J Pediatr Surg. 2007;42:806-811

IV fat emulsions and Intestinal Failure Associated Liver Disease

- **REDUCING IV fat emulsion after development of cholestasis can result in normalization of bilirubin**
  - Clayton et al. Gastroenterology 1993;105(6):1806-13
  - Colomb et al. JPEN 2000;24(6):345-350
  - Cober et al. J Pediatr 2012;160:421-427
- **LIMITING IV fat emulsion may prevent development of irreversible cholestasis**
  - Allardyce. Surg Gynecol Obstet 1982;154(5):641-647
  - Cavicchi et al. Ann Intern Med 2000;132(7):525-532
  - Shin et al. Eur J Pediatr 2008;167(2):197-202
  - Nehra et al. JPEN 2014;38(6):693-701
- **IV or enteral fish oil may prevent or reverse biochemical cholestasis**
  - Gura et al. Pediatrics 2006;118(1):e197
  - Nehra et al. JPEN 2014;38(6):693-701
  - Tillman et al. Pharmacother 2011;31(5):503-509
  - Rollins et al. Nutr Clin Pract 2010;25(2):199-204
  - Sharma. JPEN 2010;34(2):231
- **liver fibrosis may persist or progress despite normalization of bilirubin; but <u>may not progress to end stage liver disease</u>**
  - Soden et al. J Pediatr 2010;156:327-31
  - Mercer et al. JPGN 2013 56(4):364-369
  - Nandivada et al. Ann Surg 2013;00:1-8

Concerns with lipid minimization?

Essential fatty acid deficiency

Colomb et al. JPEN 2000;24(6):345-350
- 10 children (6 mo-14 yr) with IFALD, 23 episodes of cholestasis
- stopped IL in 20 episodes; **3 developed EFAD** after 3 months

Cober et al. J Pediatr 2012;160:421-427
- surgical patients in NICU (31 compared to 31 historical controls)
- decreased soy fat emulsion to 1 gm/kg twice weekly
- **8 with mild EFAD** (triene:tetraene >0.05); no clinical signs

Rollins et al. J Pediatr Surg 2013;48:1348-1356
- surgical neonates (15 in each group: soy 1 gm/kg/day vs 3 gm/kg/day)
- **none with EFAD** clinically or biochemically

Calkins et al. JPEN. 2014;38(6):682-692
- 10 infants received fish oil vs 20 historical controls
- **none with EFAD** (triene:tetraene 0.01-0.03)

Nehra et al. JPEN. 2014;38(6):693-701
- surgical infants (9 fish oil, 10 soy, both at 1 gm/kg/day)
- **none with EFAD** (median triene:tetraene 0.029 vs 0.020)

Concerns with lipid minimization?

Growth

Colomb et al. JPEN 2000;24(6):345-350
- stopped IL in 20 episodes; **decrease in weight gain in all**

Cober et al. J Pediatr 2012;160:421-427
- decreased soy fat emulsion to 1 gm/kg twice weekly
- **no difference in avg daily wt gain (13.55 ± 12.38 g IFER vs 13.25 ± 13.81 g)**

Rollins et al. J Pediatr Surg 2013;48:1348-1356
- surgical neonates (15 in each group: soy 1 gm/kg/day vs 3 gm/kg/day)
- **no difference in avg daily wt gain (20.8 g vs 23.7 g)**

Calkins et al. JPEN. 2014;38(6):682-692
- 10 infants received fish oil vs 20 historical controls
- **mean weight z-scores comparable at baseline and end of study**

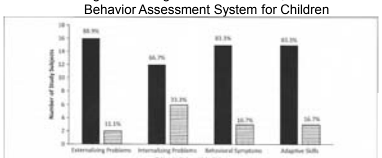
Nehra et al. JPEN. 2014;38(6):693-701
- surgical infants (9 fish oil, 10 soy, both at 1 gm/kg/day)
- **no difference in weight for age, length for age, or head circumference for age Z-scores, but trend down in weight for age Z-scores in soy group**

Concerns with lipid minimization?

Neurodevelopment

Nehra et al. JPEN 2014;38(6):693-701
- surgical infants (9 fish oil, 10 soy, both at 1 gm/kg/day)
- based on Bayley at 6 and 24 mos corrected age and Parent Report of Children's Abilities-Revised at 24 mos
  - **cognitive, language, and motor outcomes similar**
  - **verbal and nonverbal cognition similar**
- **Bayley scores were similar to expected population mean**

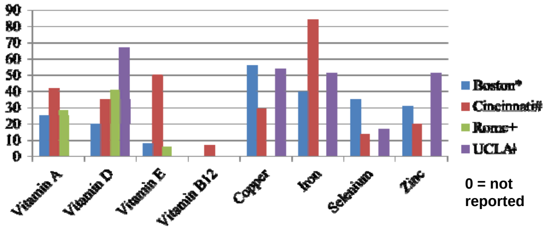
Blackmer et al. JPEN 2015;39:34-46
- 25 of 62 treated with IV fat emulsion reduction as infants evaluated
- on average received 1 gm/kg three times a week of soy emulsion
- enteral nutrition provided 12-25% of calories for 1st 6 weeks of IFER
- Ages and Stages Questionnaire-3, Parent Evaluation of Developmental Status, Behavior Assessment System for Children



BASC-2PRS-P risk categorization
■ Not at Risk
▤ At risk

Most patients "not at risk" Variables related to lipid reduction not associated with negative outcome

Micronutrient deficiencies while on some PN



*Yang et al. High prevelance of micronutrient deficiences in children with intestina failure: a longitudinal study. J Pediatr 2011;159:39-44.
#Ubesie et al. Multiple micronutrient deficiencies among patients with intestinal failure during and after transition to enteral nutriton. J Pediatr 2013;163:1692-1696.
+Diamanti et al. Fat-soluble vitamin deficiency in children with intestinal failure receiving home parenteral nutrition. JPGN 2014; 59:e46.
‡Bechtold et al. Incidence and risk factors for nutritional deficiencies in children with intestinal failure receiving home parenteral nutrition. JPEN 2015;39:242-243.

Deficiencies reported due to shortages

Copper
- periosteal reaction of humeri, femurs, some ribs and scapulae in 5 month old with no copper in PN (level <10 µg/dl)
- Oestreich and Cole. Pediatr Radiol 2013;43:1411-1413

Selenium
- 5 patients completely PN dependent had levels <20 ng/ml (nl 70-150) during shortage
- no clinical evidence of adverse effects
- Davis, Javid, Horslen. JPEN 2014;38:115-118

Zinc
- 7 infants with clinical evidence of zinc deficiency (dermatitis) after receiving PN with no zinc during shortage
- zinc level confirmed to be low in 6/7 (not tested in 7th who improved with enteral zinc supplement)
- Ruktanonchai et al. MMWR 2014;63:35-37

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Copper deficiency due to inadequate intake or excess losses

Copper deficiency
- anemia, neutropenia
- osteopenia, periosteal reactions, flaring of ribs, cupping long bones
- growth retardation, depigmentation of hair

Multiple reports of copper deficiency due to decrease or removal from PN due to cholestasis
- Blackmer and Bailey. JPEN 2013;28:75-86 (3 cases). Dembinski et al. Clin Pediatr 2012;51:759-62 (3 cases). Hurwitz et al. Nutr Clin Pract 2004; 19:305-308 (4 cases). Oestreich and Cole Pediatr Radiol 2013;43:1411-1413 (1 case). Marquardt et al. Pediatr 2012;130:e695-698 (1 case)

Copper levels in cholestatic infants and children
- 2 of 28 on standard copper with increased level
  - Frem et al. JPGN 2010;50:650-654.
- 10 of 23 on standard copper with low level
  7 of 14 on increased copper and 2 still with low level
  - Corkins et al. JPEN 2013;37:92-96

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Aluminum

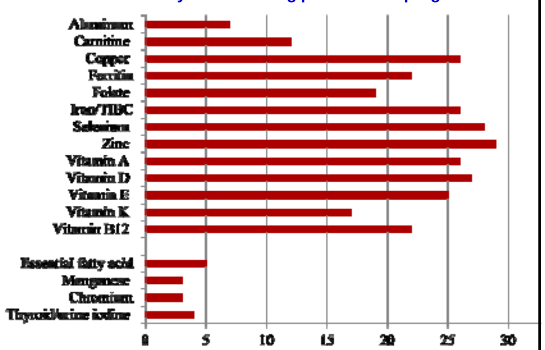
FDA mandate
- goal of less than 5 µg/kg/day of aluminum
- not possible in <50 kg child in one review (Poole et al. JPEN 2008;32:242-246)

Sources
- calcium and phosphorus higher in aluminum
- albumin
- water

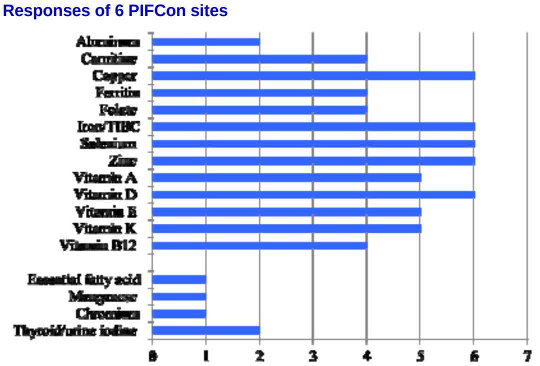
Increased risk
- renal insufficiency

Canada
- no regulations regarding aluminum content
- 27 long-term IF patients – all with elevated aluminum level (1195 ± 710 nMol/L vs 142 ± 62 in normal controls)
- Courtney-Martin et al. JPEN 2015;39:578-585

Results of informal survey of monitoring pattern of 29 programs



Responses of 6 PIFCon sites



Suggested monitoring frequency

	6 PIFCon Sites	NASPGHAN/CDHNF*	ESPGHAN/ESPEN#
Aluminum	q1mo/qyr		
Carnitine	q1mo/q3-6mo/qyr	q6-12mo	
Copper	q1mo/q3-6mo/q6mo/qyr	q6-12mo	
Ferritin	q1mo/q3-6mo/q6mo		q1-3mo
Folate	q3-6mo/q6mo/qyr	q6-12mo	
Iron/TIBC	q1mo/q3mo/q3-6mo/q6mo		
Selenium	q1mo/q3-6mo/q6mo/qyr	q6-12mo	
Zinc	q1mo/q3mo/q3-6mo/q6mo	q6-12mo	q1-3mo
Vitamin A	q3mo/q3-6mo/q6mo/qyr	q6-12mo	q6-12mo
Vitamin D	q3mo/q3-6mo/q6mo	q6-12mo	q6-12mo
Vitamin E	q3mo/q3-6mo/q6mo/qyr	q6-12mo	q6-12mo
Vitamin K	q3mo/q6mo/qyr	q6-12mo	
Vitamin B12	q3-6mo/q6mo/qyr	q6-12mo	
Essential Fatty Acid	q1mo		
Manganese	q6mo		
Chromium	q6mo		
Thyroid study/iodine	q6mo	q6-12mo	q1-3mo

*Pediatric Parenteral Nutrition Slide set. CDHNF/NASPGHAN 2011
#Guidelines on Paediatric Parenteral Nutrition of ESPGHAN and ESPEN. JPGN 2005;41:S73

Bone problems

potential risk factors

- prematurity
- inadequate calcium and phosphorus intake given solubility issues in PN
- inadequate vitamin D, vitamin K
- metabolic acidosis
- aluminum
- inflammation

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Bone problems

Khan et al. J Pediatr Surg 2015;50:136-139

- 65 pts, 34 males
- mean duration of PN 44 months
- 34% with low bone mineral density (Z-score ≤ -2) by DXA (dual energy x-ray absorptiometry)
- 42% with low vitamin D; did not correlate with low bone mineral density (BMD)
- low weight for age Z-score, low serum calcium correlated with low BMD
- low BMD did not predict fracture risk

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Bone problems

Demehri et al. J Pediatr Surg 2015;50:958-962

- 36 pts, 21 males
- duration of PN 5.1 $\pm$ 5.4 years
- DXA at age 6 years; 25 off PN by time of first DXA
- metabolic bone disease = Z-score <-1
- mean lumbar spine BMD Z-score -1.16 $\pm$ 1.32
- 64% with low vitamin D
- 11% pathologic fracture, 19% bone pain
- only significant predictor of low BMD – years on PN
- no correlation with gest age, vitamin D, calcium, PTH, cholestasis, small bowel length, IF etiology

Bone problems

Mutanen et al. Horm Res Paediatr 2013;79:227-235

- 41 pts
- duration of PN 30-69 months (11 still on PN)
- lumbar spine or femoral BMD Z-score $\leq$-1 in 70%
- 41% with low vitamin D
- duration of PN, time after weaning PN, and calcium intake predicted decreased lumbar spine BMD

Bone problems

Ubesie et al. JPGN 2013;57:372-376

- 80 pts had DXA
- 12.5% with Z-score $\leq$ -2
- 40% of larger cohort (123 pts) with low vitamin D
- no correlation of vitamin D and low BMD
- age over 10 years and exclusive PN correlated with low vitamin D and low BMD

Bone problems

Derepas et al. JPEN 2015;39:85-94

- 13 IF patients, 20 controls
- osteocalcin, bone specific alkaline phosphatase, c-telopeptide measured
- IF patients had lower osteocalcin and c-telopeptide
- osteocalcin and c-telopeptide correlated negatively with BMD

Bone problems

evidence that bone mineral density is low in significant number of those with IF

- DXA routinely done in 8 of 29 responding IF groups
- range of timing of getting DXA
  - start at age 3yrs-4yrs-5yrs-6yrs
  - then every 1yr-2yrs-3yrs

BMD does not appear to correlate with vitamin D status in pediatric studies

BMD may correlate with calcium

Renal problems

limited data in pediatrics

nephrolithiasis associated with oxaluria

GFR decreases over time in proportion to duration of PN

potential risk factors

- nephrotoxic drugs
- infections
- amino acid load
- chronic dehydration
- sodium depletion

Renal problems

Moukarzel et al. J Pediatr 1991;119:864-868

- 13 children, 8 males
- PN 7.9 ± 4.1 years
- GFR 65.5 ± 11.9 ml/min/1.73m^2
- 6 with decreased renal size on ultrasound
- normal BUN, creatinine, and urinalysis
- creatinine insensitive marker

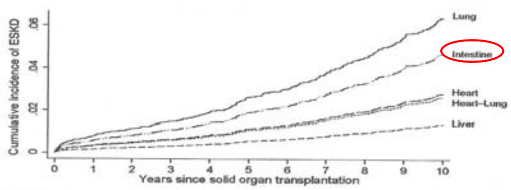

FIGURE 1
Cumulative incidence of ESKD among pediatric SOT recipients, treating death as a competing risk for ESKD.

Baseline pretransplant GFR ml/min/1.73 m^2 in 957 pts (1990-2010)

46%	≥ 90
30%	60-89
11%	30-59
3%	<30 or acute dialysis
10%	missing data

Ruebner et al. Pediatr 2013;132:31319-1326

Summary

Survival is improving

Lipid strategies (lipid minimization, fish oil)

- at 1 gm/kg/day has not resulted in biochemical or clinical EFAD
- not adversely impacted growth
- early data suggests does not impact neurodevelopment – more data needed

Micronutrient deficiencies

- appear to be relatively frequent – more data needed
- monitoring – what, when, how often is not clear

Summary

Bone problems

- decreased bone mineral density exists
- when and how often to screen is less clear
- strategies to prevent or minimize not definitive

Renal problems

- limited data but compelling evidence of reason for concern
- attention to avoidance or minimization of contributing factors (nephrotoxic drugs, dehydration, sodium depletion) is prudent

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