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


IV fat emulsions and Intestinal Failure Associated Liver Disease

- **REDUCING** IV fat emulsion after development of cholestasis can result in normalization of bilirubin
  - Colomb et al. JPEN 2000;24(6):345-350
- **LIMITING** IV fat emulsion may prevent development of irreversible cholestasis
  - Nehra et al. JPEN 2014;38(6):693-701
- IV or enteral fish oil may prevent or reverse biochemical cholestasis
  - Nehra et al. JPEN 2014;38(6):693-701
  - Sharma. JPEN 2010;34(5):526-531
- Liver fibrosis may persist or progress despite normalization of bilirubin; but may not progress to end stage liver disease
  - Soden et al. J Pediatr Gastroenterol Nutr 2010
  - Naja et al. JPEN 2011;35(6):534-539
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

- surgical patients in NICU (31 compared to 31 historical controls)
- decreased soy fat emulsion to 1 gm/kg twice weekly
- 8 with mild EFAD (meio-linolenic >0.05); no clinical signs

- 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)

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**Growth**

Concerns with lipid minimization?

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

- decreased soy fat emulsion to 1 gm/kg twice weekly
- no difference in avg daily wt gain (13.35 ± 12.38 g IFER vs 13.25 ± 13.81 g)

- 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

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**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 first 6 weeks of IFER
- Ages and Stages Questionnaire-3, Parent Evaluation of Developmental Status, Behavior Assessment System for Children

Most patients “not at risk”
Variables related to lipid reduction not associated with negative outcome
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)

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

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

Copper levels in cholestatic infants and children
- 2 of 28 on standard copper with increased level
  -From et al. JPEN 2010;30:660-664
  - 10 of 23 on standard copper with low level
  - 7 of 14 on increased copper and 2 still with low level
  -Carillo et al. JPEN 2010;37:50-56

Micronutrient deficiencies while on some PN


### 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

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### Results of informal survey of monitoring pattern of 29 programs

![Graph showing the monitoring pattern of various elements in 29 programs.]

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### Responses of 6 PIFCon sites

![Graph showing responses of 6 PIFCon sites on various elements.]

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Suggested monitoring frequency

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>NASPGHAN/CDHNF*</th>
<th>ESPGHAN/ESPFEN#</th>
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</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>q1mo</td>
<td>q6-12mo</td>
</tr>
<tr>
<td>Carnitine</td>
<td>q1mo/q3-6mo/qyr</td>
<td>q6-12mo</td>
</tr>
<tr>
<td>Copper</td>
<td>q1mo/q6mo</td>
<td>q1-3mo</td>
</tr>
<tr>
<td>Ferritin</td>
<td>q1mo/q3-6mo</td>
<td>q1-3mo</td>
</tr>
<tr>
<td>Folate</td>
<td>q1mo/q6mo</td>
<td>q6-12mo</td>
</tr>
<tr>
<td>Iron/TIBC</td>
<td>q1mo/q3mo/q6mo</td>
<td>q6-12mo</td>
</tr>
<tr>
<td>Selenium</td>
<td>q1mo/q3-6mo/qyr</td>
<td>q6-12mo</td>
</tr>
<tr>
<td>Zinc</td>
<td>q1mo/q6mo/qyr</td>
<td>q6-12mo</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>q3-6mo/q6mo/qyr</td>
<td>q6-12mo</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>q3-6mo/q6mo/qyr</td>
<td>q6-12mo</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>q3-6mo/q6mo/qyr</td>
<td>q6-12mo</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>q3-6mo/q6mo/qyr</td>
<td>q6-12mo</td>
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<tr>
<td>Vitamin B12</td>
<td>q3-6mo/q6mo/qyr</td>
<td>q6-12mo</td>
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<tr>
<td>Boiling Fatty Acid</td>
<td>q1mo</td>
<td>q6-12mo</td>
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<tr>
<td>Manganese</td>
<td>q6mo</td>
<td>q6-12mo</td>
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<td>q6-12mo</td>
</tr>
<tr>
<td>Thyroid study/iodine</td>
<td>q6mo</td>
<td>q6-12mo</td>
</tr>
</tbody>
</table>

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

Bone problems

- 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
Bone problems
- 36 pts, 21 males
- duration of PN 5.1 ± 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 ± 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
- 41 pts
- duration of PN 30-69 months (11 still on PN)
- lumbar spine or femoral BMD Z-score < -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 < -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

- 13 children, 8 males
- PN 7.9 ± 4.1 years
- GFR 65.5 ± 11.9 ml/min/1.73m²
- 6 with decreased renal size on ultrasound
- normal BUN, creatinine, and urinalysis
- creatinine insensitive marker

Baseline pretransplant GFR ml/min/1.73 m² in 957 pts (1990-2010)
- 46% > 90
- 30% 60-89
- 11% 30-59
- 3% <30 or acute dialysis
- 10% missing data

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