Parenteral Nutrition and Liver Disease

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Objectives

- Describe the pathophysiology of PNALD and the basis for proposed therapies
- Describe the novel pharmacological approaches for treating PNALD under investigation
- Describe the use of ω3-rich lipid sources as a potential method of prevention and treatment for PNALD
Parenteral Nutrition Associated Liver Disease

- Range of liver abnormalities
  - Steatosis
  - Steatohepatitis
  - Cholestasis
  - Cirrhosis
  - Portal hypertension
PNALD

- Risk factors
  - Prematurity
  - GI surgery/short gut
  - Duration of PN
  - Sepsis
  - Lack of enteral/oral intake
  - IUGR (neonates)
  - Excess amino acid intake
  - PN composition
    - $\omega$6 PUFA, phytosterols
PNALD - Pathophysiology

- Short gut, sepsis
  - Animal data – increased proinflammatory cytokines produced in setting of short gut and infection
  - Bacterial endotoxins

- Lack of enteral nutrition
  - Decreased gut hormone secretion
  - Decreased bile flow, biliary stasis


PNALD - Incidence

● Earlier reports of very high incidence
  ● 65% of adults with elevated liver enzymes after median 6 months
  ● 42% of adults complicated liver disease after median 17 months
    ● Cirrhosis, bilirubin > 60 µmol/L, encephalopathy or complications of portal hypertension
  ● Not similar population to current practice
    ● Most >1g lipid/kg/day

● More data suggests ~10-15% will develop liver abnormalities on long term PN

C Chung et al. *Clin Liver Dis* 2002; 6: 1067
PNALD - Incidence

- Younger age – increased incidence
  - Related to immaturity of liver in neonates, esp. preemies
    - 2/3 of neonates on PN will develop total bili > 34µmol/L
    - Can develop within 2 weeks
PNALD - Incidence

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>N</th>
<th>Transplanted</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;34µmol/L, but decreased to normal</td>
<td>57</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&gt;34µmol/L, no decrease</td>
<td>19</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

RA Cowles et al.  *J Ped Surg* 2010; 45: 84
PNALD - Prevention

- Standard approaches
  - Early enteral nutrition
  - Control of bacterial overgrowth
  - Lipid dosing <1g/kg/day
  - Minimizing total energy intake from PN
  - Cycling PN
PNALD – Prevention/Treatment

- Novel approaches
  - Ursodeoxycholic acid
    - Synthetic bile acid
    - Useful in other cholestatic liver diseases
    - Neonates and children
      - Two pilot studies suggesting benefit, but no benefit in a very small controlled trial
  - Adults
    - No controlled trials
    - Less consistent evidence of benefit
    - Excellent side effect/safety profile

PNALD – Prevention/Treatment

- UDCA

Liver

- Cholesterol
  - (chenodeoxy-) cholic acids
  - Taurine conjugation

Gall bladder (empties on feeding)

Duodenum

Ileum

Systemic circulation

- 95%
- 5%

Portal circulation

- 90%
- 10%

Feces
PNALD – Prevention/Treatment

● Novel approaches
  ● CCK-octapeptide
    ● GI hormone that increases gallbladder contractility and increases bile flow; no benefit in a controlled trial in children
  ● Erythromycin
    ● Antibiotic and motilin agonist used for promotility characteristics; may have some benefit in very low birthweight infants
  ● N-Acetyl Cysteine
    ● Methionine may have role in hepatotoxicity; single promising case series

DH Teitelbaum et al.  *Pediatrics* 2005; 115: 1332
PC Ng et al.  *Gastro* 2007; 132: 1726
PNALD – Fish Oil

- Why blame soy-based lipids for PNALD?
  - Observational data
    - Cholestasis worsens with increasing dose of soy oils
    - Cholestasis improves with decreasing or discontinuing soy lipids

V Colomb et al.  *JPEN* 2000; 24: 345
PNALD – Fish Oil

- Why blame soy-based lipids for PNALD?
  - Evidence of increased oxidative stress
    - Animal models – ROS can damage hepatocytes and cause cholestasis
    - Humans – large amounts of ω6 PUFAs from soy oils contains little α tocopherol or other antioxidants
      - Increases levels of peroxidation markers

MG Roma et al. *Ann Hepatol* 2008; 7: 16
PNALD – Fish Oil

- Why might fish oils be any improvement?
  - Animal model showing decreased inflammatory enzymes with parenteral ω3s
  - Animal models showing attenuation of fatty liver and prevention of steatosis
  - Fish oils contain high amounts of DHA and EPA
    - Increase production of anti-inflammatory cytokines
      - Leukotrienes B5, C5, D5
      - Prostaglandin E3, I3
      - Thromboxane A3
    - Decrease TNFα and IL6

SL Yeh et al. *Nutrition* 1997; 13: 32
PNALD – Fish Oil

Omega 3
α-linolenic acid
(18:3ω3)

EPA
(20:5ω3)

DHA
(22:6ω3)

Omega 6
linoleic acid
(18:2ω6)

AA
(20:4ω6)

docosapentanoic acid
(22:5ω6)

Omega 9
oleic acid
(19:1ω9)

Eicosatrienoic Acid
(20:3ω9)

Δ6 desaturase

Elongase

Δ6 desaturase

β-oxidation
## PNALD – Fish Oil

<table>
<thead>
<tr>
<th></th>
<th>Intralipid</th>
<th>Liposyn II</th>
<th>ClinOleic</th>
<th>SMOF Lipid</th>
<th>Omegaven</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oil Source (g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soybean</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Safflower</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>MCT</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Olive Oil</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>Fish Oil</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
<td>10</td>
</tr>
<tr>
<td><strong>α tocopherol (mg/L)</strong></td>
<td>38</td>
<td>NR</td>
<td>32</td>
<td>200</td>
<td>150-296</td>
</tr>
<tr>
<td><strong>Phytosterols (mg/L)</strong></td>
<td>348±33</td>
<td>383</td>
<td>327±8</td>
<td>47.6</td>
<td>0</td>
</tr>
<tr>
<td><strong>Fat Composition (g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linoleic</td>
<td>5.0</td>
<td>6.5</td>
<td>0.9</td>
<td>2.9</td>
<td>0.1-0.7</td>
</tr>
<tr>
<td>αlinolenic</td>
<td>0.9</td>
<td>0.4</td>
<td>0.1</td>
<td>0.3</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>EPA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>1.28-2.82</td>
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<tr>
<td>DHA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.05</td>
<td>1.44-3.09</td>
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<tr>
<td>Oleic</td>
<td>2.6</td>
<td>1.8</td>
<td>2.8</td>
<td>2.8</td>
<td>0.6-1.3</td>
</tr>
<tr>
<td>Palmitic</td>
<td>1.0</td>
<td>0.9</td>
<td>0.7</td>
<td>0.9</td>
<td>0.25-1</td>
</tr>
<tr>
<td>Stearic</td>
<td>0.35</td>
<td>0.34</td>
<td>0.2</td>
<td>0.3</td>
<td>0.05-0.2</td>
</tr>
<tr>
<td>Arachadonic</td>
<td>0</td>
<td>0</td>
<td>0.03</td>
<td>0.05</td>
<td>0.1-0.4</td>
</tr>
</tbody>
</table>
PNALD – Fish Oil

- Soy oil has been primary lipid used in PN since introduction
  - 2005 – first reported use of Omegaven monotherapy
  - 2006 – case reports of reversal of PNALD and cholestasis in infants by switching from soy lipid to fish oil

KM Gura et al. *Pediatrics* 2006; 118: e197
PNALD – Fish Oil

- 2009
  - Open label trial of Omegaven
    - 42 infants receiving soy based lipid for SBS
    - Bilirubin >34 µmol/L
    - 19/42 had reversal of cholestasis
      - Compared to control group 2/49 (historic)
      - Occurred 6x faster
      - 0/42 receiving fish oil went on to transplant vs 2/49
      - No EFAD deficiency, growth retardation, hypertriglyceridemia or coagulopathy

PNALD – Fish Oil

PNALD – Fish Oil

PNALD – Fish Oil

- Two randomized controlled trials are currently being done
  - Soy lipid (Intralipid) vs fish oil (Omegaven)PN in neonates and infants requiring PN >3 weeks ([http://www.clinicaltrials.gov/ct2/show/NCT00512629](http://www.clinicaltrials.gov/ct2/show/NCT00512629))
    - Started in Boston in 2007
PNALD – Fish Oil

- Is there any reason to be cautious about the use of fish oil as lipid source?
  - EFAD
    - ALA and linoleic acid are not supplied by 100% fish oil
    - EFAD has not been seen in children on Omegaven
    - No evidence that this is generalizable to older children or adults, nor to patients on long-term home PN

PNALD – Fish Oil

• Is there any reason to be cautious about the use of fish oil as lipid source?
  • Idiosyncratic reactions
    • Hemolytic anemia developed in an infant on Omegaven for PNALD
      ▪ 8 red cell transfusions
    • Transfusions discontinued after Omegaven stopped
    • 6 months after discontinuation, normal blood smear
    • Theorized to be due to changes in red cell membrane lipid composition

HS Mallah et al.  *J Pediatr* 2010; 156: 324
PNALD – Fish Oil

- Confounding factors – phytosterols
  - Plant sterols, only found in vegetable sourced lipids
  - Found in increased levels in serum of children with PNALD
  - In both animal and in vitro models, can be directly hepatotoxic
  - Is the benefit of fish oil the addition of $\omega 3$ or removal of phytosterols?

PT Clayton et al. *Nutrition* 1999; 14: 158
Conclusions

- Despite new and exciting advances in prevention and treatment of PNALD, prevention and treatment depends, not on a single intervention, but a multidisciplinary approach to correcting modifiable risk factors, recognizing unmodifiable risk factors, and early intervention (nutritional and pharmacological) to prevent end stage liver disease, liver transplant, and death.
Conclusions

- PNALD is likely different in adults and children, as the pathophysiology of PNALD seems to be different
  - Be wary of extrapolating data from pediatric studies to adults
Conclusions

- Sources of $\omega$3 fatty acids are an exciting new development in prevention/treatment of PNALD
  - Currently available only on compassionate release/special application from Health Canada
  - Good evidence (and even more evidence coming) for use in neonates and infants
  - Need some controlled data in adults before assuming benefit is same
"Large doses of fish oil are very good for your heart. Especially when you get the urge to swim upstream."