Identification and Management of Intestinal Failure-Associated Liver Disease (IFALD)

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Conflict of Interest

ArTara Therapeutics: Shareholder (2%)
Liver Test Abnormalities During PN

• First identified as early as 1971
• May occur in as many as 2/3 of patients parenterally fed for 2 wks or more
• Rise may be transient, peaking at 3-5 wks except AP and remain elevated for 1-4 wks after PN stopped
• Bilirubin not generally elevated
• Insensitive and nonspecific indicators of hepatic pathology
Mean Plasma Bilirubin Concentration, AST, and Alkaline Phosphatase Activity in Patients Fed for at Least 4 Weeks

Clark et al. JPEN 15:54, 1991
Chronic Cholestasis* During PN

*2 or more: ALT  
AST  
Alk Phos  >1.5 x ULN > 6 mos.

IFALD
Complicated Liver Disease*

*Definition: extensive portal fibrosis or cirrhosis, bili ≥ 3.5mg/dl for ≥ 1m, ascites, portal HTN, hepatic encephalopathy or factor V < 50%

# Prevalence of IFALD in Infants

Direct hyperbilirubinemia (>2mg/dl) is the most specific predictor of outcome

<table>
<thead>
<tr>
<th>Group</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Infants</td>
<td>7.4 – 8.4%</td>
</tr>
<tr>
<td>PN &gt; 2 weeks</td>
<td>33%</td>
</tr>
<tr>
<td>PN &gt; 3 months</td>
<td>67%</td>
</tr>
</tbody>
</table>

Pereira et al, 1981; Bell et al, 1985; Vileisis et al, 1979; Beale et al, 1979; Sondheimer, J, 1998:
IFALD - Definition

- Liver injury resulting from intestinal malabsorption and/or PN solutions in the absence of other etiologies including viral/autoimmune hepatitis, alcohol/drugs, and/or biliary obstruction

Adapted from Lal et al, Clin Nutr; 2018:1794-7
IFALD

Definition

“a persistent elevation of liver enzymes, alkaline phosphatase and γ-glutamyl transferase 1.5x the upper limit reference range which persist for more than or equal to 6 months in adults and more than or equal to 6 weeks in children.”

Diagnosis of IFALD

• Imaging or histology with steatosis / cholestasis

OR

• Imaging & biochemical evidence of cholestasis
  – (↑ bili or ALP)

• Exclusion of other hepatic pathology
## Comparison of Pathophysiology and Risk Factors of IFALD vs NAFLD

<table>
<thead>
<tr>
<th>IFALD</th>
<th>NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe nutrient and medication malabsorption</td>
<td>No nutrient or medication malabsorption</td>
</tr>
<tr>
<td>Parenteral nutrition required</td>
<td>Patients on PN excluded</td>
</tr>
<tr>
<td>↓ Plasma-free choline concentration</td>
<td>Normal or ↑ plasma-free choline concentration</td>
</tr>
<tr>
<td>No obesity, BMI normal to low</td>
<td>Obesity prevalent</td>
</tr>
<tr>
<td>↓ Plasma cholesterol concentration</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Metabolic syndrome not reported</td>
<td>Metabolic syndrome common</td>
</tr>
<tr>
<td>No insulin resistance</td>
<td>Insulin resistance present</td>
</tr>
<tr>
<td>No known cause by medications</td>
<td>Several medications can cause NAFLD</td>
</tr>
</tbody>
</table>

Buchman et al, Semin Liver Dis; 37:1-12, 2017
### Comparison of Epidemiology and Natural History of IFALD vs NAFLD

<table>
<thead>
<tr>
<th>IFALD</th>
<th>NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>65% Prevalence in the long-term PN population</td>
<td>&lt; 1% Prevalence in Long-tern PN patients</td>
</tr>
<tr>
<td>15-34% Death rate within 1-4 years</td>
<td>Rapid onset of death is extremely rare post-diagnosis</td>
</tr>
<tr>
<td>Cirrhosis develops in as little as 3-5 months after chronic PN is initiated</td>
<td>Cirrhosis takes 10-20 years to develop</td>
</tr>
</tbody>
</table>

Buchman et al, Semin Liver Dis; 37:1-12, 2017
## Comparison of Histological Characteristics of IFALD vs NAFLD

<table>
<thead>
<tr>
<th>IFALD</th>
<th>NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestasis</td>
<td>No Cholestasis</td>
</tr>
<tr>
<td>Macro- and Microsteatosis</td>
<td>Predominately Macrosteatosis</td>
</tr>
<tr>
<td>Steatosis in Zone 1</td>
<td>Steatosis in Zone 3</td>
</tr>
<tr>
<td>Features of biliary obstruction (portal inflammation, edema, ductular proliferation); ductopenia</td>
<td>No features of biliary obstruction or ductopenia</td>
</tr>
<tr>
<td>Steatohepatitis rare</td>
<td>Steatohepatitis Common</td>
</tr>
<tr>
<td>“Jigsaw” pattern of fibrosis</td>
<td>Sinusoidal fibrosis; ballooned hepatocytes with Mallory-Denk bodies</td>
</tr>
</tbody>
</table>

Buchman et al, Semin Liver Dis; 37:1-12, 2017
Macrosteatosis with Steatosis (Steatocholestasis)
Macro and Microsteatosis
Cirrhosis in IFLAD (not always present)

Fibrosis begins with portal expansion and may progress to cirrhosis, often in a characteristic “jig-saw” pattern. Masson Trichrome stain demonstrating collagen (blue) surrounding hepatocytes (red) which have a cirrhotic pattern.
Risk Factors for IFALD

< 100 cm of residual intestine: Cit < 20 µmol/ml, FGF19 <107 pg/ml

**NOT:** serum C4/total bile salts (e.g. not hepatotoxic accumulation of bile salts)

No colon in continuity

Amt of daily lipid or energy in HPN

TPN-ASSOCIATED CHOLESTASIS

Incidence: 55% after 5 years

Small bowel
- <50 cm: 44
- 50-100 cm: 23
- 100-150 cm: 15
- >150 cm: 20
- Intact: 38

Colon
- None: 40
- Partial: 52
- Intact: 45

* p=0.0014  + p=0.0013

Chambrier et al, JPEN, 1998
Prediction of IFALD Development

Model for End-Stage Intestinal Failure (MESIF)

12.05 x citrulline + 12.09 x FGF19 + 3.29x #infusions per wk

Where:  
cit > 20 = 0; < 20=1
FGF19 : 107=0; < 107=1
5 yr survival:  80% for 3-20
58% for 20-40
14% for > 40 pts

Prevention of IFLAD

• Avoid overfeeding
• Preserve intestinal length / re-anastomosis of colon
• Maintain oral intake
• Cycle PN
• Limit lipid to ≤ 1g/kg/d (no prospective study)
• Avoid sepsis?
Free of Liver Complications

Probability of Being Free of Complications

Lipid Intake, n

< 1 g/kg/d  72  59  52  41  32  28
≥ 1 g/kg/d  18  10  8   4   2   1

Carnitine Deficiency

- Plasma carnitine levels remain normal for up to 20 days on TPN, then decline and return to normal rapidly following reinstitution of oral feeding. (Hahn et al. Amer J Clin Nutr. 36:569, 1982)

- 35% of 37 pts had low plasma carnitine, but only 1 of 5 who has a bx had low hepatic carnitine and hepatic steatosis (Bowyer et al. Amer J Clin Nutr. 43:85, 1986)

- No improvement in AST, Alk Phos, Plasma TG, hepatic FFA or grade of hepatic steatosis on light microscopy despite increasing plasma carnitine levels. (Bowyer at al. Gastro. 94:934, 1988)

- No effect on FFA oxidation (Bowyer et al. Amer J Clin Nutr. 48:618, 1989)
Treatment of IFALD

No FDA-approved treatments

- Fish Oil-Based Emulsions (FOE) approved as an energy source for pediatric patients with IFALD (bili > 2 mg/dl), not as a treatment
- FOE not shown to prevent IFALD
- Not demonstrated that effects related to FO vs lipid reduction
- 1g/kg/d
Fibrosis Persists Despite FOE

- ↓ Bili, cholestasis
- ↓ Inflammation
- ↑→ Fibrosis
- ↑↓ Ductal proliferation
- ↑↓ Steatosis

Mercer et al, JPGN; 56:364-9, 2013
Choline—A Key Essential Nutrient

- An essential nutrient recognized in 1998, ubiquitous in the normal diet, mostly as phosphatidylcholine (interchangeably known as lecithin) in eggs, meat, nuts, and vegetables (1).

- Quaternary amine, methyl donor in many metabolic reactions, similar to B-vitamins and folate.

- Necessary for cell membrane structure (phospholipids), triglyceride transport via VLDL synthesis, cholesterol transport in bile, intracellular messaging, brain development and function (acetylcholine). 95% stored in tissues as phospholipids.

- Synthesis from the potential precursor amino acid methionine is impaired by parenteral (vs enteral) delivery route to the liver (3,4).

- Not included in PN products in sufficient amounts; recognized by ASPEN as needed but unavailable as a commercial PN product (2).

- Essential for cell health and survival: hepatocytes die from apoptosis in choline-deprived medium; (5) Increased DNA damage and apoptosis in lymphocytes in choline-deficient vs normal humans, (6) consistent with increased liver cancer rates in rodents after long-term choline depletion.

(1) Buchman Gastroent 2009;137:S119-S128  
(3) Stegnik et al Science 1972;178:514-516  
(5) Shin et al J Cell Biochem 1997;64:196-208  
Choline Deficiency Drives Hepatobiliary Injury in PN-Dependent Patients

~De Novo choline production supplies a maximum of 30% of needs...

... is partially reliant on exogenous choline and subject to mutations...

... choline shortage leads to impaired VLDL fat transport and pathological fat build-up in hepatocytes...

... and creates toxic bile salt activity

Stegink and Den Besten, Science, 1972
Impaired De Novo Synthesis Is At Conversion of GPCho to PCho

Choline Deficiency – Hepatobiliary Pathologies

Diminished levels of biliary phosphatidylcholine adversely affects multiple hepatobiliary functions

**Steatosis**

- Phosphatidylcholine (PC) is a critical substrate / phospholipid in VLDL package and transport
- Microvesicular accumulation of fat in the hepatocyte is differentiated from NASH
- IFALD progression to fibrosis more rapid (1)

**Cholestasis**

- PC comprises ~ 40% of bile’s organic matter (4)
- Insufficient PC in bile decreases vesicle/mixed micelle formation with cholesterol, increasing free bile salts (5)
- Free bile salts exert detergent activity on cholangiocytes, restricting bile flow (6)
- Pathophysiology similar to MD3r transporter deletion. MD3r is the only transporter of PC into the bile (7)

**Cell Death**

- Choline is an important source for intracellular signaling intermediates (2)
- Choline deficiency induces fragmentation of DNA in hepatocytes in culture (3)
- Hepatocytes die (apoptosis) in choline-deficient medium

1) Buchman et al. (2017) Semin Liver Dis
4) Schmitz MGJ, Renooij W. Gastroenterology 1990;99:1292–1296
5) Barrios and Lichtenberger (2000) gastroenterology;118:1179–1186
FIGURE 3. RELATIONSHIP BETWEEN HEPATIC FAT AND PLASMA FREE CHOLINE LEVEL

r = .60
p = .03
| Taurine | Methionine | Cysteine | 1/2 Cystine | Protein-bound Cysteine | Glutathione | Free Choline | Free Carnitine | Total Carnitine | Creatine | Phosphatidyl Choline
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>69.4 ± 8.3</td>
<td>31.9 ± 2.6</td>
<td>11.2 ± 0.9</td>
<td>79.4 ± 7.9</td>
<td>150.6 ± 5.3</td>
<td>4.5 ± 0.4</td>
<td>12.8 ± 0.8</td>
<td>48.5 ± 2.7</td>
<td>62.0 ± 2.6</td>
<td>32.7 ± 2.7</td>
<td>71.7 ± 5.9</td>
</tr>
<tr>
<td>69 ± 4.3</td>
<td>59.0 ± 20.6</td>
<td>6.9 ± 1.1</td>
<td>88.6 ± 22.4</td>
<td>153.5 ± 16.9</td>
<td>47 &lt; 1</td>
<td>7.1 &lt; 1</td>
<td>7.1 ± 0.9</td>
<td>7.1 ± 0.9</td>
<td>7.1 ± 0.9</td>
<td>73 ± 5.9</td>
</tr>
<tr>
<td>6.1 ± 0.9</td>
<td>78.0 ± 67.4</td>
<td>7.8 ± 1.0</td>
<td>84.3 ± 27.0</td>
<td>160.8 ± 13.6</td>
<td>60 ± 1.7</td>
<td>6.0 ± 1.7</td>
<td>58.3 ± 10.2</td>
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<td>26.7 ± 12.8</td>
</tr>
<tr>
<td>6.1 ± 0.9</td>
<td>143.2 ± 254.2</td>
<td>5.7 ± 1.0</td>
<td>72.4 ± 7.6</td>
<td>97.8 ± 12.1</td>
<td>2.7 ± 0.9</td>
<td>2.7 ± 0.9</td>
<td>73.6 ± 31.0</td>
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<td>73.6 ± 31.0</td>
<td>124.7 ± 37.2</td>
</tr>
<tr>
<td>6.1 ± 0.9</td>
<td>9 ± 0.9</td>
<td>2 ± 0.2</td>
<td>2 ± 0.2</td>
<td>2 ± 0.2</td>
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<td>2 ± 0.2</td>
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</tr>
</tbody>
</table>

**Healthy controls on mixed foods (N=14)**

**Cirrhotic Patients**

<table>
<thead>
<tr>
<th>Vivonex</th>
<th>Mixed</th>
<th>p</th>
<th>N</th>
<th>TPN</th>
<th>p</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>82.9 ± 25.3</td>
<td>47.9 ± 4.3</td>
<td>1 &lt; .05</td>
<td>10</td>
<td>6</td>
<td>31.0 ± 5.1</td>
<td>1 &lt; .05</td>
</tr>
<tr>
<td>183.0 ± 67.4</td>
<td>59.0 ± 20.6</td>
<td>1 &lt; .005</td>
<td>10</td>
<td>6</td>
<td>143.2 ± 254.2</td>
<td>1 &lt; .005</td>
</tr>
<tr>
<td>7.8 ± 1.0</td>
<td>6.9 ± 1.1</td>
<td>1 &lt; .05</td>
<td>10</td>
<td>6</td>
<td>5.7 ± 1.0</td>
<td>1 &lt; .05</td>
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<td>1 &lt; .05</td>
<td>10</td>
<td>6</td>
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<td>1 &lt; .005</td>
</tr>
<tr>
<td>160.8 ± 13.6</td>
<td>153.5 ± 16.9</td>
<td>1 &lt; .001</td>
<td>10</td>
<td>6</td>
<td>97.8 ± 12.1</td>
<td>1 &lt; .001</td>
</tr>
<tr>
<td>60 ± 1.7</td>
<td>47 &lt; 1</td>
<td>1 &lt; .01</td>
<td>6</td>
<td>2</td>
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<td>1 &lt; .001</td>
<td>5</td>
<td>2</td>
<td>37.0 ± 37.9</td>
<td>1 &lt; .001</td>
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</table>

**Fasting** TPN values are determined from plasma samples drawn at 8 AM.

Significance level based on comparison to average value of normals on mixed foods.

Thirty normal subjects were assayed for plasma glutathione levels.

Normal Choline Concentration Reached/Sustained

![Graph showing plasma free choline concentration over assessment weeks]

- **p<0.05
- *p<0.01

Assessment Week:
- Plasma Free Choline Concentration (mmol/mL)

Choline D/C’d:
- BL
- 2
- 4
- 6
- 12
- 16
- 20
- 24
- 34
CT converted to MRI-PDFF:
- \[ \text{MRI-PDFF (\%) = -0.572}\times\text{Liver CT (HU)} + 37.264(1) \]

Comparing groups on the relative (%) change of MRI-PDFF, drug-PBO differences from Weeks 4-24 were large and clinically meaningful (range 31%-54%).

2019 Oley UI Health Combined Conference

June 21–24 • Marriott Resort Lincolnshire
Cholestasis - Sustained Improvement Throughout Study in IFALD-Defining Pathology

- Pronounced treatment effect as measured by reduction in alkaline phosphatase (ALP) levels
- Subgroup analyses of ALP >1.5ULN demonstrated clinically meaningful improvement (20-30%)
Is a Second Hit Necessary?

Serum AST conc

Serum TNF conc

Histology:
- CS/S
- CS/LPS
- CD/S
- CD/LPS
- CD/Ab/LPS

## Is a Second Hit Necessary?

<table>
<thead>
<tr>
<th>Diet Administered</th>
<th>Treatment</th>
<th>Macrovascular Fatty Changes</th>
<th>Hepatonecrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS</td>
<td>Saline</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CS</td>
<td>Bacterial Endotoxin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CD</td>
<td>Saline</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CD</td>
<td>Bacterial Endotoxin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CD</td>
<td>Bacterial Endotoxin, Single Dose of Anti-TNF-α IgG</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Changes in Serum Free Choline Concentrations in Response to Endotoxin

Ilcol et al, Shock 24:288-93, 2005
Methionine Toxicity

Chow Group I
TPN/Lipids Group II
Chow + IV Methionine Group III

Groups II, III
- Decreased bile flow
- Balloon degeneration of hepatocytes and eosinophilic infiltration of portal triads
- ↑ Homocysteine

Moss et al, J Pediatric Res; 45:664-8, 1999
How to Follow a Patient with IFLAD?

- Serial MR?
- Elastography – No
- Serial biopsies – probably not
- Labs
  - ↑ bili in adult → Tx eval

- Should be NO liver/intestine transplants
Severity of IFALD

• Degree of fibrosis ?
• Ultra-short gut; ethanol; diabetes
  (Cazals-Hatem Liver Int 2018; 38:174-82)
• The great unknown
Cumulative Survival

Days

CRP

CRP < 1 mg/dl

1 ≤ CRP < 4 mg/dl

4 ≤ CRP < 8 mg/dl

CRP ≥ 8 mg/dl

Development of Fibrosis

- Ultra-short bowel (RR 12.4, p < 0.001)
- ETOH (RR 7.4, p = 0.009)

Non-Factors

- PN composition
- PN duration
- Episodes of sepsis

Cazels-Haten et al, Liver Int; 38:174-82, 2018
What Makes Staging Difficult?

• Pathogenesis of IFALD is multifactorial
  – Some more clinically significant than others
• Pathogenesis of IFALD may be multi-step process and the severity of sequelae of the underlying pathogenesis may have variable degrees of clinical significance
  – Steatosis → Steatohepatitis → Cirrhosis or Hepatic Failure
• Animal models do not reflect the complexity of humans
• Some etiologies of IFALD may be reversible and others not, and the degree of reversibility as well as the time frame of reversibility may be variable
Staging Criteria

- Hepatic aminotransferases - insensitive/nonspecific
- Drug or dye elimination – may reflect selected parts of liver function including blood flow, P450, etc.
- Histology (severity of fibrosis, severity of inflammation, degree of steatosis)
- MELD, PELD, Child, Pugh, Puke
The Problem?

- Difficulty in the differentiation of severe, but reversible liver disease from that which is irreversible
- Predict those who are more likely to survive a transplant, but do not transplant prematurely
IFALD Treatment Summary

- Eat
- Re-anastomose colon to residual small bowel
- Intestinal rehabilitation – diet, hormonal, ORS
- Decrease lipid emulsion to <1gm/kg/d
- Keep dextrose <4-5mg/kg/min
- UDCA?
- FOE?
- Choline (investigational)
- Isolated intestinal transplantation
- Liver/small bowel transplantation