Treatment of Intestinal Failure:
Where have all the yellow babies gone?

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Capetown SA, March 2012
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Alberta Children’s Hospital
Objectives

• Intestinal Failure
  – What is it? Who gets it?
  – What are the complications?

• The Long Road to Intestinal Autonomy
  – What is Intestinal Adaptation?
  – How can we stimulate Intestinal Adaptation?
  – How can we prevent complications of IF?
  – Results of a standardized protocol

• New Hope
  – Fish oil, olive oil, the novel lipid emulsions
  – S.T.E.P. procedure
  – GLP-2

Strategies in Low and Middle Income Countries
Intestinal Failure: Definitions

• Critical reduction in *functional* gut mass below minimal amount necessary for adequate digestion and absorption to satisfy nutrient and fluid requirement for growth:
  • Small bowel < 40 cm
  • Continuous Parenteral Nutrition requirement > 42-60 d

Goulet JPGN 2004 38(3):250-69, Kocohis JPGN 2004 29(S2)S655-61
Intestinal Failure

• Incidence: 1200/100,000 live births
• Survival rates: 73-89%

• Etiology SBS in Canada:
  – Intestinal Atresia: 30%
  – Volvulus 10%
  – Gastrochisis 12.5%
  – NEC 35%

IF: Risk factors

RF: PNAC
- Prematurity
- Low birth weight
- Perinatal depression/shock
- Male gender
- Infection: Sepsis, SBBBO
- Enzyme deficiencies
- Genetic causes
- Lack of/diminished enteral intake
- Duration of PN
- Components of PN

RF: Mortality on PN
- Prematurity, young age
- Poor mucosal integrity, ischemia
- No ICV, <25 cm SB
- Intractable diarrhea
- Early catheter infections (< 3 mo)
- >3 CVL infections or >1 /mo
- > 3.5 g/kg/d lipid (soybean)
- Lack of enteral feeding
- Lack of specialist staff


IF: Goal: to stimulate **Adaptation of Remnant Intestine**

- **Short segment**
  - Nutrients
  - Diminished SA
  - Reduced Nutrient Absorption
  - Diarrhea
  - Mucosal Inflammation
  - Dehydration
  - Electrolyte disturbance
  - Perianal excoriation

- **Adapted Intestine**
  - Increased Nutrient Absorption
**Intestinal Adaptation: Mechanisms**

- ↑ **Surface area**: due to ↑ villus height
- ↑ **Crypt Cell Proliferation**, ? ↓ **Apoptosis**
- **no ↑** in nutrient transporter density
- **Overtime**: ↓ in proximal secretion, ↓ in transit rates
- **Adaptation only occurs in response to** **feeding**
- **Clinically may take** 6 to 18 months

(Micrographs X40 of ileal mucosa following 90% resection, pair fed enterally, Martin, Sigalet et al AJP, 2005)
Intestinal Adaptation

**HORMONAL FACTORS**
- Enteroglucagon
- Glucagon-like peptide 2
- Peptide YY
- Secretin
- Growth Hormone
- Growth Factors: IGF-1, polyamines

**DIETARY FACTORS**
- Trophic feeds
- Long chain TG
- Protein
- Glutamine
- Pre-biotics, probiotics
- SCFA-butyric acid

Primary Driver of Adaptation? GLP-2

GLP-2 Receptor

† Motility
† CCPR
Trophic ++

L-cell

Nutrients

Cell renewal zone

Villus
Epithelium

Goblet cells

Absorptive cells

Cell division

Crypt
Epithelium

Cell exclusion zone

Blood vessels
Lymph vessels
Nerves
Smooth muscle
Connective tissue
Lymphocytes
Plasma cells
Eosinophiles

Muscularis mucosa
IF: Complications

- PN associated liver disease (PNALD)
  - Steatosis, cholestasis, cirrhosis
- CVL related complications
  - Septicemia, fungemia, thrombosis
- Gastrointestinal (function & length)
  - Dysmotility
    - Hypermotility
      - Malabsorptive Diarrhea, fluid and electrolyte abnormalities, micronutrient deficiencies
    - Hypomotility
      - Small bowel bacterial overgrowth
  - Gastric hypersection
  - Allergic/inflammatory
I.F. Survival <-> Prevention of PNALD

Quiros-Tegeira, J Peds 2004
Causes of Complications in Post-Surgical IF

Short segment

Nutrients -

Diminished SA

Distension Vomiting

"Over- Adaptation"
Dilated/ poor motility

"Leaky Gut"

Bacterial overgrowth

Sepsis

Cholestatic Liver

Inflammation (cytokines)

STASIS

Undigested Nutrients

TPN Lipids (ω-6, Intralipid)
An ounce of prevention.....
IF Therapy: Promote Adaptation
Prevent PN Associated Liver Disease

Short segment $\leftrightarrow$ Adaptation

1. Feeds: Breast Milk or Neocate
2. Protocol Based Feeds: Monitor Output
3. Re-feeding of Stoma
4. Rotating Antibiotics/Motility Agents
5. Lipid Reduction PN
6. $\omega$-3 (Fish Oil Based) Lipid Preparations
7. STEP Procedure

STASIS

Undigested Nutrients

"Leaky Gut"

Bacterial overgrowth

Sepsis

TPN Lipids ($\omega$-6, Intralipid)

Cholestatic Liver

Inflammatory Cytokines
Management

- Lack of evidence based protocols
- Requires micromanagement

"You know, I REAL-L-L-L-L-Y hate it when he micromanages."
Study Methods:

• Compare Outcomes of Two Treatment Protocols for Pediatric Surgical Intestinal Failure
  – Patients managed by: primary surgeon, Pediatrics + GI consultation: No consistent protocol
  – 2006-2009 (CHIRP) Data: Prospective, Consistent Treatment Protocol
  – All patients managed until discharge by CHIRP team
  – Team: Peds Surgeon, GI, nursing, Dietician, OT, Social Work
  – Definitions: Intestinal Failure
    • < 40 cm of small intestinal length
    • PN Requirement for > 42 days
  – Liver Failure: Bilirubin >100 umol/L for 2 months or more
  – Ethics approval: 16506: “Monitoring outcomes in Pediatric Short Bowel Syndrome”
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<th>Parameter</th>
<th>98-06</th>
<th>2006-09</th>
<th>P value</th>
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<tr>
<td>number</td>
<td>33</td>
<td>31</td>
<td></td>
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<tr>
<td>Birth Weight (grams)</td>
<td>2480±600</td>
<td>1980±910</td>
<td>NS</td>
</tr>
<tr>
<td>Gest. Age (weeks)</td>
<td>33.7±3.4</td>
<td>32.9±4.8</td>
<td>NS</td>
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<tr>
<td>Gest. age at surgery</td>
<td>35±12</td>
<td>35.6±6.6</td>
<td>NS</td>
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<tr>
<td>Small bowel length (cm)</td>
<td>59±33</td>
<td>95±46</td>
<td>&lt;0.02</td>
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<tr>
<td>Small bowel length (% predicted)</td>
<td>62±33</td>
<td>71±30</td>
<td>&lt;0.02</td>
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<tr>
<td>Ileocecal valve resected</td>
<td>7/33</td>
<td>6/31</td>
<td>NS</td>
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<tr>
<td>Colon Resected</td>
<td>11/33</td>
<td>6/31</td>
<td>NS</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
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<tr>
<td>Gastroschisis</td>
<td>10</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Atresia/Atresia + Gsc</td>
<td>7/4</td>
<td>5/4</td>
<td>NS</td>
</tr>
<tr>
<td>NEC</td>
<td>10</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>4</td>
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## Treatments by Era

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<tr>
<th>Parameter</th>
<th>98-06</th>
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<tbody>
<tr>
<td>Number</td>
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<td>31</td>
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<tr>
<td>Rotating Antibiotics</td>
<td>5 (15%)</td>
<td>22 (71%)</td>
<td>0.01</td>
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<tr>
<td>Lipid reduction strategy</td>
<td>2 (7%)</td>
<td>18 (58%)</td>
<td>0.04</td>
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<tr>
<td>Fish oil based lipids</td>
<td>0</td>
<td>14 (45%)</td>
<td>0.001</td>
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<tr>
<td>STEP procedure</td>
<td>0</td>
<td>4 (13%)</td>
<td>0.03</td>
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Data: subjects receiving intervention/total subjects in the group. P values from Fisher’s exact test.
Outcomes by Era

Liver Function over Time

Time to Liver Failure  P<0.01
Outcomes by Era

Patient Survival

Patients censored at death or at last follow-up.
P<0.02
Outcomes by Era

Time to Intestinal Autonomy

- **98-06** Mean 4.5±3.2
- **06-09** Mean: 4.3±3.8

Patients censored when off of PN, or at death
06-09 Cohort: Complications During Therapy

• Bilirubin/Liver Function/PT/Platelets: Normal after 3 months of Lipid reduction/Fish oil based therapy
• Z Scores: -1.3 at start of therapy→+0.4 after PN discontinued for 2 months
• 1 patient: Clinical Fatty acid deficiency on fish oil based mono-therapy, normalized with combined intralipid/omega-
  • No developmental problems on screening
Conclusions...

- 06-09 CHIRP Protocol: Improved survival, due to reduced incidence of liver failure
- Specific cause: not clear → further study required, especially of effects of Fish-oil based PN
- Multi-disciplinary team invaluable
- No improvement in time to adaptation
- Limitations: partially retrospective design,
  ↑ Intestinal length in recent cohort
  ↓ Follow up in recent cohort
New Hope: Novel Medical and Surgical Therapy
FA & Inflammation

<table>
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<tr>
<th>OMEGA-6 FAT</th>
<th>OMEGA-3 FAT</th>
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<tr>
<td>Linoleic acid</td>
<td>Linolenic acid</td>
</tr>
<tr>
<td>▼ GLA (gamma linolenic acid)</td>
<td>▼ EPA (eicosapentaenoic acid)</td>
</tr>
<tr>
<td>▼ AA (arachidonic acid)</td>
<td>▼ DHA (docosahexaenoic acid)</td>
</tr>
<tr>
<td>▼ pro-inflammatory prostaglandins and leukotrienes</td>
<td>▼ anti-inflammatory prostaglandins and leukotrienes</td>
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ALTED IMMUNE & INFLAMMATORY PHENOTYPE

Wanten G et Am J Clin Nutr 2007 85:1171
# Novel Lipid Emulsions

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<tr>
<th></th>
<th>n-6/n-3</th>
<th>α-tocopherol (µmol/L)</th>
<th>phytosterols</th>
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<tbody>
<tr>
<td>Intralipid 20%</td>
<td>7:1</td>
<td>87</td>
<td>348 ± 43 mg/L</td>
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<tr>
<td>Clinoleic 20%</td>
<td>9:1</td>
<td>75</td>
<td></td>
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<tr>
<td>Omegaven 20%</td>
<td>1:8</td>
<td>505</td>
<td>0</td>
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<tr>
<td>SMOF</td>
<td>2.5:1</td>
<td>500</td>
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Potential Therapy for SBS: GLP-2

Phase 1-2 Trial Underway
Surgical Therapy for IF
S.T.E.P.

- 33% decrease width
- 300% increase in SA/Volume

Kim et al J Ped Surg 2003;38:881
Serial Transverse Enteroplasty Procedure

Intestinal Length
• Pre-STEP 46 cm
• Post-STEP 91 cm

International STEP Registry

• 19 centers n=38
• Indications:
  – SBS, SBBO, neonatal atresia with marginal bowel length
• Early complications:
  – Post-op bowel obstruction (n=2), abscess (n=1), hematoma (n=1)
• Late complications:
  – Progression to liver transplant (n=3), death from end stage liver failure (n=3)
    - High rate of re-dilation (>60%)
    - Use only with true “short” length; otherwise suggest tapering

Nutritional Support in LM Income Countries

Intralipid: $5/500 mls       Omegevan: $25/100 mls (25x )
Nutritional Support in LM Income Countries

- Transanastomotic Feeding tubes:
- Low cost → $5/tube
- Principle: leave a feeding tube past anastomosis into functional small bowel
  - via NG (low risk)
  - Via Gastrostomy (Intermediate)
  - Jejunal tube (higher risk)
Nutritional Support in LM Income Countries

Refeed →

Objectives

• Intestinal Failure
  – What is it? Who gets it? \(\rightarrow\) Atresias, GSc, NEC
  – What are the complications? \(\rightarrow\) PNALD

• The Long Road to Intestinal Autonomy
  – What is Intestinal Adaptation? \(\rightarrow\) \(\uparrow\)Crypt cell Proliferation \(\uparrow\) Surface Area
  – How can we stimulate Intestinal Adaptation? \(\rightarrow\) Feed Breast milk
  – How can we prevent complications of IF? \(\rightarrow\) Feed Breast milk
  – Results of this protocol \(\rightarrow\) 100% Survival

• New Hope
  – Fish oil, olive oil, the novel lipid emulsions \(\rightarrow\) New lipids!
  – S.T.E.P. Procedure \(\rightarrow\) Very rarely useful \(\rightarrow\) Tapering
  – GLP-2 \(\rightarrow\) Stay tuned

Strategies in Low and Middle Income Countries \(\rightarrow\) Transanastomotic Feeding Tubes
The C.H.I.R.P. Team: