Intestinal Rehabilitation at CHLA
Pediatric Intestinal Failure

• Definition: **Need for Parenteral Nutrition for >60 days** due to intestinal disease, dysfunction or resection

• Most commonly a feature of short bowel syndrome

• Other causes
  – Chronic intestinal pseudo-obstruction syndromes
  – Congenital enteropathies
  – Lymphatic malformations
  – Unresolved complex surgical problems
    • Fistulas
    • Strictures
  – Radiation enteritis (rare in childhood)

NASPGHAN (Merritt et al, JPGN 2017)
Pediatric Short Bowel Syndrome

• **Definition**: Need for *parenteral nutrition* >60 days after bowel resection, or residual small bowel length <25% expected

• Most cases neonatal

• 25 per 100,000 births; many are premature

• Most common causes
  – Gastroschisis
  – Necrotizing enterocolitis
  – Malrotation with volvulus
  – Intestinal atresias

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1 NASPGHAN (Merritt et al JPGN 2017)
2 Wales et al J Pediatr Surg 2004
There are 3 Types of Short Bowel Syndrome

Type 1

Type 2

Type 3

Drawings from Short Bowel Support website
Intestinal Rehabilitation Programs

- Centers of excellence
- **Comprehensive team approach**
- Emphasis on prevention/amelioration of complications
- Implementation of cutting edge therapies
- Outcomes tracking and reporting
- Platform for clinical research
Intestinal Rehabilitation Programs in the Management of Pediatric Intestinal Failure and Short Bowel Syndrome

*Russell J. Merritt, †Valeria Cohran, ‡Bram P. Raphael, §Timothy Sentongo, ||Diana Volpert, 
*#Brad W. Warner, and **Praveen S. Goday, on behalf of the Nutrition Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

What Is Known

- Intestinal failure is a debilitating condition that presents both acute and chronic medical management challenges.
- Intestinal Rehabilitation Programs exist in multiple sites across North America and Europe.

What Is New

- Management of intestinal failure by Intestinal Rehabilitation Programs is the current state of the art, with limited but highly encouraging, supporting data on their medical efficacy.
- NASPGHAN endorses management of patients with intestinal failure by, or in consultation with, centers with intestinal rehabilitation programs and encourages further research on the medical efficacy, patient satisfaction and quality of life, and financial impact of intestinal rehabilitation programs.
### TABLE 2. Members of pediatric Intestinal Rehabilitation Programs

<table>
<thead>
<tr>
<th>Professionals</th>
<th>Role and services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric surgeons</td>
<td>Gastrointestinal surgery, central venous catheter procedures. Inpatient and outpatient surgical management</td>
</tr>
<tr>
<td>Transplant surgeons</td>
<td>Assessment, surgery, immunosuppression</td>
</tr>
<tr>
<td>Pediatric gastroenterologists</td>
<td>Inpatient and outpatient medical management</td>
</tr>
<tr>
<td>Neonatologists</td>
<td>Initial inpatient management of premature and critically ill infants</td>
</tr>
<tr>
<td>Interventional radiologists</td>
<td>Central venous line management</td>
</tr>
<tr>
<td>Gastroenterology/parenteral nutrition nurses</td>
<td>Line and ostomy care, education</td>
</tr>
<tr>
<td>Pharmacists</td>
<td>Supervision, preparation of parenteral nutrition, drug-nutrient interactions</td>
</tr>
<tr>
<td>Registered dietitians</td>
<td>Nutritional monitoring and counseling, drug-nutrient interactions</td>
</tr>
<tr>
<td>Social workers</td>
<td>Access available resources; support</td>
</tr>
<tr>
<td>Physical/occupational/speech</td>
<td>Feeding, mobility and development</td>
</tr>
<tr>
<td>Therapists</td>
<td>Child and family support, education</td>
</tr>
<tr>
<td>Child-life specialists</td>
<td>Individual treatment and family support</td>
</tr>
<tr>
<td>Psychologists</td>
<td>Instruction on self-care</td>
</tr>
<tr>
<td>Medical educators</td>
<td></td>
</tr>
</tbody>
</table>
Intestinal Rehabilitation Teams Can Really Improve Care\textsuperscript{1-3}

• **Survival improved**
  – Infants with IF
  – Patients not weaned from TPN
  – Patients with liver failure
  – Patients referred for transplant

• **Less Morbidity**
  – Lower rates of CLABSI
  – More rapid achievement of enteral autonomy
  – More patients removed from transplant waiting list improved

• **What teams do differently**
  – More frequent lipid modification
  – Reduce progressive liver disease
  – More STEP procedures
  – More treatment of bacterial overgrowth
  – Higher percentage of transplant wait list transplanted

\textsuperscript{1}Stranger et al J Pediatr Surg 2013
\textsuperscript{2}Wales et al JPEN, 2014
\textsuperscript{3}NASPGHAN (Merritt et al JPGN 2017)
Goals of Pediatric Intestinal Rehabilitation

- Promote intestinal adaptation and achieve enteral autonomy before complications of IF prove lethal
- Support growth and development
- Improve survival and quality of life
- Manage transition from parenteral to enteral feedings
- Prevent macro and micronutrient deficiencies
- Minimize complications of IF and nutrition support

¹NASPGHAN (Merritt et al JPGN 2017)
Preserve as Much Bowel as Possible

• Minimize initial gut resection
  – Second look operations
  – Gastrochisis “parking”

• Preserve ileo-cecal valve, colon when possible

• Early reanastomosis, when possible

• Consider lengthening procedures rather than resection or tapering procedures

Promote Bowel Adaptation

- Feed to the point of some diarrhea
- Accept outputs of 30-40 ml/kg/d
- Replace electrolyte and fluid losses as needed
- More adaptation possible with bowel continuity
- Consider bowel lengthening procedures
- Explore new therapies to promote bowel growth
Grow More Bowel—Support “Adaptation”

- Hormones and nutrients
  - Growth hormone--FDA approved in adults
  - Teduglutide--FDA approved in adults (& kids in EU)
  - IGF-1-- No clinical trials
  - Modified enteral insulin—No clinical trials
  - Epidermal growth factor—No clinical trials
  - Glutamine
  - Omega-3 fatty acids
Role of Glucagon-like Peptide-2 (GLP-2) in Bowel Adaptation
Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome

Brett A. Carter, MD, Valeria C. Coletti, MD, MS, Conrad R. Cole, MD, MPH, MSc, Mark R. Corkins, MD, Reed A. Dinnitt, MD, MPH, Christopher Duggan, MD, MPH, Susan Hill, MRCPath, DM, Simon Roseman, MB, ChB, FRCPCH, Joel D. Lim, MD, David F. Mercer, MD, PhD, FRCS, Raseel J. Morriss, MD, Peter E. Nicholl, MD, PNO, Luther Sigurdsson, MD, Daniel H. Terkelbaum, MD, John Thompson, MD, Charles Vanderpool, MD, Julianna F. Vaughan, MD, Benjamin Li, MS, Nadir Yousef, MD, Robert S. Versick, MD, and Samuel A. Kokoshis, MD

Objective To determine safety and pharmacodynamic/efficacy of teduglutide in children with intestinal failure associated with short bowel syndrome (SBS-F).

Study design This 12-week, open-label study enrolled patients aged 1-17 years with SBS-F who required parenteral nutrition (PN) and showed minimal or no advance in enteral nutrition (EN) feeds. Patients enrolled sequentially into 3 teduglutide cohorts (0.0125 mg/kg/d [n = 8], 0.025 mg/kg/d [n = 14], 0.05 mg/kg/d [n = 15]) or received standard of care (SOC, n = 26). Descriptive summary statistics were used.

Results All patients experienced ≥1 treatment-emergent adverse event; most were mild or moderate. No serious teduglutide-related treatment-emergent adverse events occurred. Between baseline and week 12, prescribed PN volume and calories (kcal/kg/d) changed by a median of -41% and -45%, respectively, with 0.025 mg/kg/d teduglutide and by -20% and -32%, respectively, with 0.05 mg/kg/d teduglutide. In contrast, PN volume and calories changed by 0% and -6%, respectively, with 0.0125 mg/kg/d teduglutide and by 0% and -1% with SOC. Per patient diary data, EN volume increased by a median of 22%, 32%, and 40% in the 0.0125, 0.025, and 0.05 mg/kg/d cohort, respectively, and by 11% with SOC. Four patients achieved independence from PN, 3 in the 0.025 mg/kg/d cohort and 1 in the 0.05 mg/kg/d cohort. Study limitations included its short-term, open-label design, and small sample size.

Conclusions Teduglutide was well tolerated in pediatric patients with SBS-F. Teduglutide 0.025 or 0.05 mg/kg/d was associated with trends toward reductions in PN requirements and advancements in EN feeding in children with SBS-F.

Trial registration ClinicalTrials.gov: NCT01952080; EudraCT 2013-004588-30
What Gattex® (Teduglutide) Does

- Stimulates bowel growth
- Increases villi length and crypt depth, intestinal mass
- Decreases stomach acid secretion & motility
- Increases net fluid and nutrient absorption
- May increase bile export
- Effects present while the drug is given
Pediatric Teduglutide Study

- 12 week study in 42 pediatric patients at 1 of 3 dose levels or SOC
- The 2 higher doses reduced PN volume and calories by 25-41%
- 4 patients came off TPN (2 restarted)
- No drug-related serious adverse events
- Overall response similar to adult studies
Access to Cutting Edge Therapies

Current Therapies
- Novel lipids
- Teduglutide
- Thrombus prevention
- Vein rehabilitation

Future Therapies?
- Fecal transplantation
- Tissue bioengineering
- New trophic hormones
Mixed-Methods Pilot Study: Disaster Preparedness of Families With Children Followed in an Intestinal Rehabilitation Clinic

Catherine J. Goodhue, MN, RN, CPNP; Natalie E. Dumeter, MPH; Rita V. Burke, PhD, MPH; Khadija T. Toor, MD; Jeffrey S. Upperman, MD; and Russell J. Merritt, MD, PhD

Improving Disaster Preparedness of Families With a Parenteral Nutrition–dependent Child

Khadija T. Toor, MD; Rita V. Burke, RN; Natalie E. Dumeter, MPH; Jeffrey S. Upperman, MD; Russell J. Merritt, MD; Choo Phee Wee, MD; and Catherine J. Goodhue

Intravenous Fish Oil Lipid Emulsion Prevents Catheter-Related Thromboses in Pediatric Patients with Intestinal Failure

Mohammad M. Jamai, MD, MPH; Vinoda Bhardwaj, MD; and Russell J. Merritt, MD, PhD

Primary intestinal lymphangiectasia with massive abdominal lymphatic malformation requiring surgical debulking


Oral Feeding Difficulties in Children With Short Bowel Syndrome: A Narrative Review

Judy Hopkins, OTD, OTR/L, CLC; Sharon A. Cermak, EdD, OTR/L, FAOTA; and Russell J. Merritt, MD, PhD

Stoned—A Syndrome of D-Lactic Acidosis and Urolithiasis

Casey M. Berman, MD; and Russell J. Merritt, MD, PhD

Chyulous ascites following Kasai portoenterostomy: Case study and review of the literature

E.M. Pontrelli, A.J. Coodhue, R.J. Merritt, and D.M. Anselmo
CHLA Intestinal Rehab and Home PN Program

Patient & family

Physician

Nursing

Nutrition

Home vendor pharmacy, therapies, subspecialists etc.

OT

Social work
Regions Served

Counties:
Los Angeles
Orange
San Diego
Riverside
San Bernardino
Kern
Santa Barbara
San Luis Obispo
Sacramento
Social Work

Provides psychosocial support to patients and families

Inpatient role:

• Say what? What did that Dr. just say?
• Plan and facilitate family team meetings and intro to team
• Link families to other families who perform same tasks at home
• Identify barriers to success and provide resources
• Advanced CVC class – an example of multidisciplinary excellence
• Difficult families: provide concrete teaching plan
Social Work

Outpatient role:

• School coordination - IEPs, 504 plans
• Dealing with trauma: Got therapy?
• Let’s get together!  Supper club, Holiday event, Education Day
• Quality of life: Painted turtle, swimming, travel
• Short gut/TPN resources: Oley Foundation, Kidz Spirit, Facebook groups
• Feeding class: Normalizing the experience of feeding difficulties and giving giving some solutions
Nutrition Support Nurse

Scope of Practice includes but is not limited to the following in directing patient care:

- Intravenous access and troubleshooting problems
- Education of patients and caregivers regarding Central line and GT/JT care
- Participation in research activities
- Transition of care
- Resource for CHLA nursing and other disciplines with Home Parenteral Nutrition

Coordination of Care: School, Home Health Agencies, DME and Pharmacy vendors, Outside support resources, Transition of care
IV access and infection prevention

--Parents attend educational Central Line, GT/JT and ostomy classes

--Designated TPN Nurse Line for parents to call

--Teaching reinforced during follow up visits.
# Draft Cribside Check List for TPN CVCs

<table>
<thead>
<tr>
<th>Observations</th>
<th>Yes</th>
<th>No</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dressing intact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressing clean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVL taped correctly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol cap on all unused ports</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVL is not near ostomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ostomy is not leaking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child cannot access CVL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vest in use if available</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Palas & Merritt, abstract presented at Nutrition Week 2018
Role of Occupational Therapy

OT practitioners:

- Address physical, cognitive, psychosocial, and sensory aspects of everyday life activities.
- Enable individuals to participate in productive and meaningful activities of daily life
- Help individuals develop age appropriate skills while fostering independence
- Develop strategies to integrate management of medical conditions into existing habits.
Infancy: early hospitalization, oral interventions to promote positive oral experiences and decrease oral aversion, positioning for play.
Infancy: early hospitalization, oral interventions to promote positive oral experiences and decrease oral aversion, positioning for play
Toddlers: developmental screening, sensory processing screening, mealtime routines, referrals as needed
School age: Transition into school, more independence with self care, social skills support
Adolescents: self care, independent living, increased knowledge of medical condition, adapting environment to maintain social connections

Transition to adult care: navigating the medical system
Predisposition to, Initiation & Perpetuation of Feeding Problems

**Predisposing factors**
- Prematurity/LBW
- Developmental delay
- Autism spectrum disorder
- Congenital poor appetite
- Sensory disorder

**Initiating factors**
- TPN
- EN
- No feeds
- Clefts
- TEF
- Aspiration event
- EOE
- GERD
- DGE
- Constipation
- Milk allergy

**Perpetuating factors**
- Spasticity

**Caregiver stress**
- Intrusive or non-responsive feeding style

**Responsive feeding style**
- Positive sensations

**Learning**
- Nociceptive stimuli

**Food refusal**
- Fear of feeding
- Gag
- Vomit
- Head Turning

**Normal caregiver developmental history**
Registered Dietitian Role in IR team

- Nutritional Assessment
- Correcting Malnutrition, promoting growth and development
- Working towards enteral autonomy, patient specific nutrition plans
- Preventing and treating Macro/Micronutrient Deficiencies
Meet Nutritional Needs to Promote Growth, Development & Quality of Life

- Feed enterally to tolerance
- Meet the rest of nutrition needs with PN
- Provide oral stimulation in attempt to preserve ability to eat
- Monitor nutritional status

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight g/day</th>
<th>Height Cm/week</th>
<th>FOC Cm/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preemie &lt; 2kg</td>
<td>15 – 20</td>
<td>0.8 – 1</td>
<td>0.8 – 1</td>
</tr>
<tr>
<td>Preemie &gt;2kg</td>
<td>20 – 30</td>
<td>0.8 – 1</td>
<td>0.8 – 1</td>
</tr>
<tr>
<td>0 – 4 mo</td>
<td>23 – 34</td>
<td>0.8 – 0.93</td>
<td>0.38 – 0.48</td>
</tr>
<tr>
<td>4 – 8mo</td>
<td>10 – 16</td>
<td>0.37 – 0.47</td>
<td>0.16 – 0.2</td>
</tr>
<tr>
<td>8 – 12mo</td>
<td>6 – 11</td>
<td>0.28 – 0.37</td>
<td>0.8 – 11</td>
</tr>
<tr>
<td>12 – 16 mo</td>
<td>5 – 9</td>
<td>0.24 – 0.33</td>
<td>0.04 – 0.08</td>
</tr>
<tr>
<td>16 – 20mo</td>
<td>4 – 9</td>
<td>0.21 – 0.29</td>
<td>0.03 – 0.06</td>
</tr>
<tr>
<td>20 – 24mo</td>
<td>4 – 9</td>
<td>0.19 – 0.26</td>
<td>0.02 – 0.04</td>
</tr>
<tr>
<td>2 – 10 y/o</td>
<td>2 – 3kg/year</td>
<td>5 – 8cm/year</td>
<td></td>
</tr>
</tbody>
</table>

[Graph: Weight-for-age BOYS (Birth to 2 years)](www.who.int/childgrowth/en)
Nutritional Considerations

Potential Nutrient deficiencies

*Duodenum*
--Iron, Folate

*Jejunum*
--Calcium, Zinc

*Ileum*
--B12, bile acids, Fat soluble vitamins (A, D, E, K)

*IC valve*
--Macronutrients
Feeds Promote Bowel Adaptation

**With oral/enteral feeding**
- Intestine grows longer
- Villi grow longer
- Bowel dilates
- Adaptation potential: premature >> term infant > child > adult
- Ileum adapts more than jejunum

**Breast milk** is and some specific nutrients may be **trophic**
- Long chain fatty acids
- Short chain fatty acids
- Glutamine
- Hormones and other growth factors

**Intestinal continuity promotes more adaptation**
- Distal small bowel & proximal colon have **L-cells** that make GLP-2 for bowel growth
Minimize Fluid Losses

Minimize fecal fluid losses (<40 ml/kg/d)

• Drip feeds may reduce diarrhea
• Gastric acid suppression
• Non-absorbable opiates
• Bile acid binders (if colon)
• Fiber (green beans)
• Avoid liquid forms of medications
Replace Excessive GI Losses

<table>
<thead>
<tr>
<th>Site</th>
<th>Daily volume*</th>
<th>Na mEq/dL</th>
<th>K mEq/dL</th>
<th>Cl mEq/L</th>
<th>HCO3 mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>1-2 L</td>
<td>60-80</td>
<td>15</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>2-5 L</td>
<td>140</td>
<td>20</td>
<td>100</td>
<td>25-50</td>
</tr>
<tr>
<td>Colon</td>
<td>0.2-0.5L</td>
<td>75</td>
<td>30</td>
<td>30</td>
<td>-</td>
</tr>
</tbody>
</table>

Usual IV replacement fluids:

Gastric: 0.5 NS + 15 mEq KCl/L
Proximal ostomy: NS + 20 mEq KCl/L
Distal ostomy: NS or 0.5 NS + 20 mEq KCl/L

*(adult values)
Pureed Green Beans

- Fiber (prebiotics) may help bowel adaptation
- Mechanisms may include:
  - Slowing motility
  - Providing bacterial/mucosal nutrition
  - Thickening bowel contents
  - Altering the microbiome and its effects
- Many fibers have been used
  - Clinicians have been frustrated with inconsistent results
  - Families and clinicians have become believers!
- Try this:
  - Mix green beans 1:2 with formula and drip X 4 hours
  - Observe effect in reducing stool volume/looseness

Drenkphol 2005
# Osmolarity of Enteral Liquid Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Osmolarity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>16100</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>8350</td>
</tr>
<tr>
<td>Furosemide</td>
<td>8975</td>
</tr>
<tr>
<td>Loperamide</td>
<td>6775</td>
</tr>
<tr>
<td>Acetomenophen</td>
<td>6425</td>
</tr>
<tr>
<td>Multivitamin</td>
<td>5700</td>
</tr>
<tr>
<td>Co-sulfamethoxazole</td>
<td>5560</td>
</tr>
<tr>
<td>Neomycin</td>
<td>5230</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>5010</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>5010</td>
</tr>
<tr>
<td>Nystatin</td>
<td>3300</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>2185</td>
</tr>
<tr>
<td>Magnesium citrate</td>
<td>1000</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>605</td>
</tr>
</tbody>
</table>

*Depends on formulation and concentration

Sources: Shikora et al, ASPEN’s *Nutritional Considerations in Intensive Care* 2002; Klang et al, JPEN 2013; Ernst et al, Pediatrics 1983; Mutz et al, Pediatrics 1985
Managing Complications that lead to Transplant or Death

2015 Transplant Indications\textsuperscript{1}
\begin{itemize}
  \item >2 admissions to the ICU
  \item Loss of \textgreater 3 central vein sites
  \item Conjugated bilirubin >4.4mg/dL despite 6 weeks of lipid modification therapy
\end{itemize}

\begin{itemize}
  \item Prevent and treat CLABSI
  \item Avoid central IV access depletion
  \item Prevent and treat IFALD
\end{itemize}

\textsuperscript{3}Burghardt, Am J Transplant 2015
Prophylaxis of Infections

• Hospital Policies for catheter care
  – “Bundle” policies and standardized nursing policies & procedures
  – Biopatch reduces infection risk
  – Caps may reduce hub contamination

• Ethanol locks
  – 5-10 fold CLABSI reduction (Mouw, Wales)
  – APSA, 2011: Reduces infections (Grade A/B)

• IR currently uses 70% ethanol locks for 2 hrs tiw
  – Silicon catheters only
  – Clear catheter of heparin first (precipitates
Deep Vein Thrombosis (DVT)

Management
• Usually treated for 3-6 months or duration of CV access
• Commonly used subcutaneous heparin agents;
  – Enoxaparin & fundaparinux
    • Monitor levels of anti-Factor Xa
• Vascular recanalization possible to preserve venous access
• Notable adverse drug effects
  – Bleeding
  – Thrombocytopenia (less with fundaparinux)
  – Osteopenia with chronic use (less with fundaparinux)

Prevention
– CHLA study found IV fish oil may prevent DVT

1Sullivan, Pediatrics, in press
2Jami, J Peds, in press
Intestinal Failure Associated Liver Disease (IFALD)

Predisposing clinical events
  – Prematurity
  – Small for gestational age
  – Weeks or months of fasting
  – Duration of TPN
  – Excessive macronutrient intakes
  – Infections
  – Gut damage and bacterial overgrowth

Progression leads to death or liver transplant
Management of IFALD

• Feed, feed, feed...
• Avoid “hyperalimentation”
• Cycle TPN if possible
  – Usually not <4 kg or without enteral feeds
• Treat bacterial overgrowth; prevent sepsis
• Start ursodiol (it improves the transaminases)
• Assess possibility of other causes of cholestasis
• Lipid modification
Lipid Modification

• Rationale
  – Evidence IV soy oil contributes to IFALD

• Choices
  – Stop IV lipid
    • Risk of EFAD
    • Need another source of EFA (formula, food oils)
  – Lipid restriction
    • 0.5 to 1 g/kg/d (vs. usual 2-3 g/kg/d)
    • Some evidence for improvement of cholestasis¹
    • Risk of EFAD
    • GIR will need to be higher
  – Change lipid source
    • Smoflipid® (not FDA-approved for pediatric use)
    • Omegaven®

¹Cober, J Peds 2012
Smoflipid®

- Composition:
  - 30% Soy
  - 30% MCT
  - 25% Olive
  - 15% Fish

- “Healthier” lipid blend
- Requires 2g/kg/d to meet EFA requirements
- Used at CHLA in premies (<28 wks GA), for intestinal failure and when PN need >14 days
Canadian Smoflipid® Pilot Study

- 24 infants with intestinal failure and early IFALD blindly *randomized* to SMOF or Intralipid
- At study end bilirubin was *significantly* lower with SMOF and *significantly* more infants had direct bilirubin=0 (p<.03)
- FDA approved in adults
- US Pediatric studies ongoing

1Diamond et al, 2016
Omegaven®

• 10% emulsion of highly refined fish oil (Omega 3-based compared Omega-6 based soy-derived Intralipid®)
• 112 Cal/100 ml
• Contains glycerol and egg yolk emulsifier (like Intralipid®)
• ~50% of lipid content is EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid)—Omega 3 fas
• Packaged in glass bottles of 50 & 100 ml
• Approved by FDA for Pediatric use July 2018
Clinical Studies of IV Fish Oil (Omegaven®) for IFALD

- Initial case report (2 patients) of Omegaven® use for IFALD from Boston (Gura et al. 2006)
- Large case series reports from Boston Children’s and Texas Children’s (Puder 2009 and Premkuman 2013) and many smaller series
  - Bilirubin up to 9 times more likely to normalize with IV fish oil (Puder)
- Cochrane Review showed efficacy for lowering direct bilirubin
- Reducing bilirubin may aid bowel adaptation
- Fewer liver transplants occurring in short gut patients (UNOS)
- No substantive clinical safety issues
- Liver fibrosis may persist (Matsumoto 2014, Imseis, 2015)
- No double-blind randomized therapeutic clinical trials
Omegaven®

What do we know

• Used in hundreds of infants under approved IRB protocols (Boston, Houston, others) and INDs.

• Shown to be safe and effective in reversing the biochemical measurements of IFALD in a majority of infants who have received it under these protocols.

• Multiple studies have shown that biochemical cholestasis and avoidance of liver transplantation occurs in ~85% of Omegaven® recipients.

• Typical time course of biochemical resolution is consistent (Premkumar et al. Adv Nutr 2014):

Texas Children’s Hospital cohort of patients (n=83)

- Group A = C Bili 2.1-5 mg/dL (n=47)
- Group B = C Bili 5.1-10 mg/dL (n=23)
- Group C = C Bili > 10 mg/dL (n=13)

• There are SOME Omegaven® recipients who fail to respond to fish oil therapy.
Omegaven®

FDA-approved July 27, 2018

What does this mean?

• Approved as an orphan drug July 27, 2018—Use approved for treatment (not prevention—likely bc not tested in prevention of IFALD)

• IRB-approval or INDs for Omegaven® protocols will not be required. May take a couple of months for Fresenius to establish distribution, pricing.

• Important to still Rx Omegaven® in a thoughtful fashion. It is not, in our opinion, the ideal IV choice for every neonate.

• Urge continued referral to Intestinal Rehabilitation Centers (such as CHLA) to help determine if Omegaven® (vs SMOF® vs Intralipid®) should be the choice for a particular patient.
What Happens When...

Things go well:
Children:
• Grow normally
• Develop normally
• Progress from IV to oral therapies

Things don’t go well:
Children are re-hospitalized with
• Dehydration
• CLABSI
• Catheter & tube problems
These lead to:
• Poor feeding progress
• IV access depletion
• Chronic liver disease
• Feeding aversions
Case 1: Background

- 27 year old Latino mother G3—P2 (prior birth at 20 weeks)
- MG Born at 28 weeks’ gestation, related to maternal bleeding. BW= 1228g
- Had mild respiratory distress and started on feeds on day 4. Feeds held d/t bloody stool. Resumed feeds on DOL 12
- Quickly advanced to goal feeds by DOL 18.
- Intermittent feeding intolerance and then suddenly advanced NEC at 3 weeks of age. Transferred to CHLA NICU at DOL 22 for higher level of care and need for surgical intervention
- Surgical resections left him with 25 cm of small bowel and ½ his colon (SBS dependent on TPN)
- Had placement of CVC and GT
Case 1: Medical Hx

- Discharged at 4 months, currently 10yrs old.
- > 30 admissions to hospital
- Meds: 9 plus Ca, Fe, D

- Special therapies:
  - IV fish oil
  - Teduglutide

Medical problems:
- Complications of Intestinal failure
  - CLABSI
  - IFALD
- Complications of Prematurity
  - CLD
  - NEC/SBS
  - ADHD
  - Mild developmental delay
  - Seizure disorder
Case 1: Nutrition Support

At time of recent visit:

- Pediasure Peptide 165 ml/hr X 18 hours
  - Mixture of (710ml) 1.5cal and (2250ml) 1.0cal
  - Including green beans x 4hrs BID

- 180 ml blenderized feed qDay using standard jarred food recipe

- TPN providing 500 Cal
  - 800 ml x8hrs, D15%, 0.8 g/kg AA

- Combined EN/PN = 3950 ml (130ml/kg), 4007 (132kcal/kg), 108g pro (3.6 g/kg)

- Oral diet → feeding aversions. Licks foods, spoonful's of purees, and drink water.
## Case 1: Nutrition Support

### Blenderized tube feedings in Short Bowel Syndrome

Yes! Thus far 3 patients with partial blenderized diets

One patient successfully weaned from his PN to enteral autonomy

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent satisfaction</td>
<td>Time/Labor intensive</td>
</tr>
<tr>
<td>Increasing diversity of prebiotic fibers in SBS pts who we know have altered microbiome</td>
<td>Food Safety concerns</td>
</tr>
<tr>
<td>Reporting similar effects as green beans, increasing stools thickness and reducing volume</td>
<td>Difficulty determining macro/micronutrient content of home recipes</td>
</tr>
</tbody>
</table>
Case 1: Weaning PN

- Started Gattex® Jan 2017
- 1 year → weaned 525kcals PN (50% ↓) and increased EN by 1012kcals (60% ↑)
Case 1: Summary

- Nutritional status: stable weight with BMI at 75%ile
- Low copper, hypervitaminosis A (MVI@50% and Cu @ 2x)
- Goals: Continue to works towards enteral autonomy (low probability)
- Plan: Increase concentration of enteral feeds
Conclusion

• **Family challenges:** Parenting styles, emotional impact of not eating, language barriers (mother has learned English), assuring special educational needs are met

• **Learning:** Issues related to prematurity do not end at hospital discharge. Growth, development and school attendance are possible with intestinal failure