Expanding Options for the Treatment of Intestinal Failure & Short Bowel Syndrome

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Disclosures

• Past medical director: J&J, Nestle and Abbott
• Retiree: Abbott Laboratories
• Stockholder: Abbott, Abbvie, J&J
• Site PI, Speaker: Takeda Pharmaceuticals
• DSBM Chair: Fresenius
• Consultant: Alcresta
Expanding Options for the Treatment of Intestinal Failure & Short Bowel Syndrome

10 Questions Worth Asking

1. Do I (or my child) need/have access to expert care?
2. Have I had a central line infection in the past 3 years?
3. How can I protect my child’s catheter?
4. How do I avoid running out of veins for catheters?
5. How can diarrhea or high ostomy output be controlled?
6. Can I do anything to keep my bowel “adapting?”
7. Am I at risk, and if so, how can I prevent kidney stones?
8. Am I getting the right IV lipid emulsion for me?
9. Am I ready for “The Big One?”
10. How can I help improve care and access to care for intestinal failure?
Expanding Options for the Treatment of Short Bowel Syndrome

10 Questions Worth Exploring

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Intestinal Rehabilitation Teams

What’s New? NASPGHAN Society Paper¹:
• “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...

Who needs to be seen by one?
• Patients with SBS not making progress toward enteral autonomy and continuing on PN >3 months, those with high clinical complexity or with worsening or non-resolving IFALD, recurrent sepsis, deep vein thrombosis or loss of venous access....”

¹R Merritt et al, Intestinal Rehabilitation Programs in the Management of Pediatric Intestinal Failure and Short Bowel Syndrome JPGN 2017
Intestinal Rehabilitation Teams Really Improve Care*

• Survival
  – Even if not weaned from TPN
  – Even with liver failure
• What teams do differently
  – More weaning from PN
  – Reduced central line infections
  – More frequent use of lipid modification
  – Reduced progressive liver disease
  – More STEP procedures
  – More likely to treat bacterial overgrowth
  – Higher percentage transplant wait list transplanted

* Reported outcomes vary by program; Merritt et al 2017
Novel Ways to Access IR Team Expertise

• Some states mandate transportation
• Telemedicine

• **LIFT-ECHO®**
  • “The heart of the ECHO model™ is its hub-and-spoke knowledge-sharing networks, led by expert teams who use multi-point videoconferencing to conduct virtual clinics with community providers. In this way, primary care doctors, nurses, and other clinicians learn to provide excellent specialty care to patients in their own communities.
  • Together, they manage patient cases so that patients get the care they need.”
• This ECHO team is led by Dr. Kishore Iyer in New York
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Have I had a Central Line Infection in the Past 3 Years?
Should I “lock” out bugs?

• Ethanol locks have been used in prevention protocols in many centers with high risk patients
  – 5-10 fold reduction in PN patients with recurrent CLABSI
  – APSA, 2011: Reduces infections
  – Potential concerns
    • Precipitates with heparin
    • May lead to catheter damage
    • One study stopped due to occlusion of ports
    • Not usually used with PICCs
    • Uninfected catheters may not last as long with 70% ethanol
• Antibiotic locks sometimes used in place of ethanol
• Taurolock™ (Liu, 2013) -- used in Europe--not available in US
More Help for preventing CLABSI

• Hospital Policies for catheter care
  – “Bundle” policies and standardized nursing policies & procedures
  – Recent meta-analysis of 79 ICU studies found a 60% reduction in catheter infection rate (Ista 2016)

• Biopatch® reduces infection risk

• Paranoia can be highly effective
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Catheters and tubes are “attractive nuisances”

Preventative actions

- Tape catheters securely
- Use ethanol caps
- Use vests to limit access to lines & tubes
- Keep catheter away from diaper & ostomies
Example of Vest for Safe TPN
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What leads to Access Depletion?

• CLABSI
• Deep vein thromboses
• Multiple catheters placed in multiple sites
• Depletion assessed by ultrasound, contrast and MR evaluations
“Evidence-Based Strategies and Recommendations for Preservation of Central Venous Access in Children”
K Baskin et al JPEN in press

• “According to the VANGUARD Affected Persons Advisory Panel, affected persons perceive that central venous access is often treated as an incidental series of episodic events until something catastrophic happens.”

• Moving forward...

  Strong Recommendation: “Prospective venous access planning should begin at the time the high-risk patient is first diagnosed with an indication for chronic access”
Vein Reconstruction of Home TPN Patients May Be Feasible

F Ing 2001
P Sullivan 2018
Can IV Fish Oil Help Prevent Deep Vein Thrombosis?

Table I. Characteristics of patients who received FOLE or SOLE

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FOLE</th>
<th>SOLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Males</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Ages</td>
<td>1 mo-18 y</td>
<td>3 mo-19 y</td>
</tr>
<tr>
<td>Percentage PICC/Broviac catheters (%)</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>Mean/median lipid exposure (d)</td>
<td>97/144</td>
<td>993/998</td>
</tr>
<tr>
<td>Receiving ethanol locks (n)</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Causes of intestinal failure (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC or SIP with SBS</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Gastrochisis or omphaloele with SBS</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Atresia or volvulus with SBS</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Trauma leading to SBS</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hirschsprung’s disease or pseudo-obstruction</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Mucosal disease</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>With CRT* (n)</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>CRT events/1000 days’ lipid exposure†</td>
<td>0</td>
<td>0.29</td>
</tr>
</tbody>
</table>

NEC, Necrotizing enterocolitis; PICC, percutaneously inserted central catheter; SBS, short bowel syndrome; SIP, spontaneous intestinal perforation.

*χ² P < .001
†χ² P = .23.
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How Can Diarrhea or High Ostomy Output Be Controlled?

- Acid suppression helpful in the first year or two
- Higher than recommended doses of loperamide sometimes used
- Cholestyramine may help--when the colon is present
- Fiber can have a role in improving bowel adaptation and reducing diarrhea
  - Slows motility
  - Thickens bowel contents
  - Provides bacterial/mucosal nutrition
  - Alters the microbiome and its effects
- Many different fibers have been used, often without success
- Recent advance: green bean puree via GT
  - Mix 1:2 with formula and drip X 4 hours
  - Consistent effect in reducing volume/looseness

Drenkohl 2005
Kerner (abs) 2019
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Role of Glucagon-like Peptide-2 (GLP-2) in Bowel Adaptation
Why a GLP-2 Agonist Might Help

• Stimulates bowel growth
• Increases villi length and crypt depth, intestinal mass
• Decreases stomach acid secretion & motility
• Increases net fluid and nutrient absorption
Gattex®

- GLP-2 hormone made in bacteria and modified to have a longer duration of action
- Administered by daily injection
- Indicated for reduction of dependence on TPN and IV hydration in adults with SBS
- FDA approved for adult in 2012 and for children >1 year of age in 2019
What Adult Clinical Studies Show

After 24 weeks, when compared to a control group:

• 63 vs 30% had ≥ 20% decrease in IV fluid\(^1\)
• 54 vs 23% decreased weekly TPN by ≥ 1 day\(^1\)
• In patients who received extended therapy
  • 13/88 graduated from TPN/IV fluid\(^2\)
  • Improvement may continue with extended therapy

\(^1\)Jeppesen, 2012
\(^2\)Schwartz 2016
\(^3\)Jeppesen abs 2012
Pediatric 24 Week Study
Percentage Change From Baseline in IV Fluid and Calories

![Graphs showing percentage change from baseline in IV fluid and calories over 24 weeks. The graphs compare standard of care with teduglutide at 0.025 mg/kg and 0.05 mg/kg.](image)

*P<0.005 vs SOC

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2019 Oley UI Health Combined Conference
June 21–24 • Marriott Resort Lincolnshire
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Who’s Most at Risk?

• Adult SBS patients with a colon
  – 24% in 5 years)
• Less is known about children with SBS
Prevention of Calcium Oxalate Stone Recurrence

Assure good hydration
Diet rich in fruits and vegetables, as feasible
Low oxalate diet
Oral calcium supplementation
Oral potassium citrate supplementation to normalize urinary citrate
Oral magnesium supplementation, as tolerated

Berman & Merritt, 2018
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# ILE Composition Comparison

<table>
<thead>
<tr>
<th></th>
<th>Intralipid&lt;sup&gt;1&lt;/sup&gt; 20% Emulsion</th>
<th>Nutrilipid&lt;sup&gt;2&lt;/sup&gt; 20% Emulsion</th>
<th>Smofilipid&lt;sup&gt;3&lt;/sup&gt; 20% Emulsion</th>
<th>Clinolipid&lt;sup&gt;4&lt;/sup&gt; 20% Emulsion</th>
<th>Omegaven&lt;sup&gt;5&lt;/sup&gt; 10% Emulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Fresenius Kabi/Baxter&lt;sup&gt;*&lt;/sup&gt;</td>
<td>B Braun</td>
<td>Fresenius Kabi</td>
<td>Baxter</td>
<td>Fresenius Kabi</td>
</tr>
<tr>
<td><strong>Oil Source</strong></td>
<td>Soybean Oil</td>
<td>Soybean Oil</td>
<td>Soybean Oil 30% MCT 30% Olive Oil 25% Fish Oil 15%</td>
<td>80% Olive Oil 20% Soybean Oil</td>
<td>Fish Oil</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Adults and Pediatrics</td>
<td>Adults and Pediatrics</td>
<td>Adults</td>
<td>Adults</td>
<td>Pediatrics</td>
</tr>
</tbody>
</table>

**Fat Composition (Mean value or range % by weight)<sup>1-7</sup>**

<table>
<thead>
<tr>
<th></th>
<th>Linoleic</th>
<th>Alpha-Linolenic</th>
<th>Eicosapentaenoic</th>
<th>Docosahexaenoic</th>
<th>Oleic</th>
<th>Arachidonic</th>
<th>Alpha-Tocopherol (mg/L)</th>
<th>Phytosterol Content&lt;sup&gt;6&lt;/sup&gt; mcg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intralipid</td>
<td>44.62</td>
<td>4.11</td>
<td>0</td>
<td>0</td>
<td>19.30</td>
<td>163-225</td>
<td>24&lt;sup&gt;+&lt;/sup&gt;</td>
<td>342.89 ± 5.87 – 439.1 ± 5.7</td>
</tr>
<tr>
<td>Nutrilipid</td>
<td>48.58</td>
<td>4.11</td>
<td>0</td>
<td>0</td>
<td>17.30</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Smofilipid</td>
<td>17.5</td>
<td>2.25</td>
<td>1.35</td>
<td>1.35</td>
<td>23.35</td>
<td>0.5</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Clinolipid</td>
<td>17.9</td>
<td>2.35</td>
<td>0</td>
<td>0</td>
<td>44.3-79.5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Omegaven</td>
<td>1.5</td>
<td>1.1</td>
<td>13.26</td>
<td>14.27</td>
<td>4.11</td>
<td>0.2-2</td>
<td>0.2-2</td>
<td>3.66 ± 0.59</td>
</tr>
</tbody>
</table>

* Distributed by ND = No Data
† Internal Data

1. Fresenius Kabi LLC USA. Intralipid 20%. Prescribing Information. 2015.
Smoflipid®

- Oil Mixture:
  - 30% Soy
  - 30% MCT
  - 25% Olive
  - 15% Fish

- “Healthier” lipid blend
- Provides 2 calories/ml
- Dose is 1-2.5 g/kg/d
- ~2g/kg/d meets EFA requirements for HTPN
- Consider use in premature infants, for patients intestinal failure and when PN need >14 days
24 infants with intestinal failure and early liver disease were randomized to SMOF or Intralipid in blinded fashion.

At study end bilirubin was significantly lower with SMOF and significantly more infants had direct bilirubin=0 (p<.03)

Diamond et al, 2016
Omegaven®

- 10% emulsion of highly refined fish oil
- Provides 1.12 Cal/ml
- Contains glycerol and egg yolk emulsifier (like soy LE)
- ~50% of lipid content is EPA and DHA
- Packaged in glass bottles of 50 & 100 ml
- Approved by FDA for pediatric IFALD when direct bili >2 in 2018
- Recommended dose is 1g/kg (most experience from infant studies)
What Do We Know about IV Fish Oil for IFALD?

- No definitive randomized controlled trials
- Multiple case series (up to 97 IFALD patients)
  Patients were up to 9 times more likely to experience fall in bilirubin
- Meta-analysis: Lowers direct bilirubin
- Lower bilirubin may help bowel adaptation and allow more time for adaptation
- Decrease in pediatric liver transplants for SBS corresponds to increased Omegaven use
- No substantive safety issues identified
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Disaster Preparedness is Possible for Home PN Patients

Family confidence of disaster readiness (10 is best)
Questions about your Disaster Preparedness

1. Does your family have a written Family Emergency Communication Plan in case you are separated during a disaster?  
   YES / NO
2. Does your family have a designated meeting place outside of your home?  
   YES / NO
3. Does your family have a designated meeting place outside of your neighborhood?  
   YES / NO
4. Does your family have an emergency supply kit that can last you for 3 days?  
   YES / NO
5. Does your family have a fire escape plan for your home?  
   YES / NO
6. Does your family keep emergency supplies in each of your vehicles? (e.g., blankets, flashlights?)  
   YES / NO
7. Does your family have 3 gallons of water stored for each person in the household (3 day supply)?  
   YES / NO
8. Does your family have enough stored food that does not need refrigeration or preparation that can sustain your family for 3 days? (if yes, go to question 9)  
   YES / NO
9. Is the food separated from your regular food supply?  
   YES / NO
10. Do you have a working flashlight with an extra set of batteries in your home?  
    YES / NO
11. Do you have a packaged first aid kit in your home?  
    YES / NO
12. Do you have a container that is both fireproof and waterproof for storing important papers in your home?  
    YES / NO
13. All family members over 14 years old know how to turn off the gas, power, and water to our household in case of an emergency  
    YES / NO
14. I have a copy of my child’s Medical Emergency Plan (Emergency Information Form) completed by his/her doctor.  
    YES / NO
15. All children over 5 years old in our house are able to state their full name, address, and phone number. YES / NO
16. How many extra days of medication do you have on hand at all times for each family member with a chronic medical condition?  
    _____ days
17. Do you have a back-up source of electricity for your child’s infusion pump?  
    YES / NO
18. Do you have additional supplies necessary for your child’s infusion system?  
    YES / NO
19. Do you have “back-up” nutrition for your child?  
    YES / NO
20. On a scale of 1-10 with 10 being the best, how confident are you that you are ready for a disaster?  
    1 2 3 4 5 6 7 8 9 10
CHLA Disaster Survival Toolkit

• Four D-cell batteries for use in HPN pumps
• Power inverter for charging laptops and phones from a car battery source
• Waterproof flash drive with the child’s medical information and instructions for a local emergency department or provider, should the child present for care (e.g., for fever, low blood sugar, dehydration, a need for alternate fluid sources, or central line damage)
• Paper copies of the same medical information, as some hospitals do not allow external information to be uploaded on their electronic medical record (EMR) systems
• Supply list (Figure 2)
• Emergency Information Form (EIF)
• Power and water discount forms for the local utilities
• Handouts from FEMA and the Red Cross specific to earthquakes.
Where to find help

**Before you need it!**


- American Academy of Pediatrics
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Support and Access to Care

• Local and national patient self-support groups
  – Locally we have “Supper Club” and “Snack Pack” and family picnics
  – Family support via KidzSpirit Foundation

• Participation in foundations (Oley!)
  – Support
  – Education and awareness
  – Advocacy

• Political action (personal and organizational)
  – Should research dollars be directed at cancer, heart disease, living on mars or intestinal failure?
  – Influence drug approval and insurance regulatory processes
  – Assure coverage for nutritional supplements, essential services