INTESTINAL REHABILITATION IN CHILDREN

Debora Duro, MD, MS

Program Director,
Pediatric Gastroenterology, Hepatology and Nutrition
Medical Director, “FIRST for Children”
Florida Intestinal Rehabilitation Support and Treatment Program
Salah Foundation Children’s Hospital at Broward Health
Fort Lauderdale, Florida, USA

Associate Professor in Clinical Pediatrics at Florida International University, Miami, FL
Associate Professor in Clinical Pediatrics at NOVA Southeastern University, Fort Lauderdale, FL
Disclosure

- Speaker Bureau for ABBOTT Nutrition
- Speaker Bureau for Fresenius Kabi
- Clinical consulting and part of speaker bureau for Kate Farms
Objectives

✓ Define Short Bowel Syndrome and Intestinal Failure and the most common causes

✓ Intestinal Rehabilitation: review new predictors that play a role to achieve enteral autonomy

✓ Intestinal Failure Associated Liver Disease (IFALD) and new era of prevention therapy

✓ Key factors to enhance bowel adaptation in Intestinal Failure and future directions…
Generating an Artificial Intestine for the Treatment of Short Bowel Syndrome

Mark L. Kovler, MD, David J. Hackam, MD, PhD,*

KEYWORDS
- Intestinal stem cells • Artificial intestine • Tissue engineering

KEY POINTS
- Intestinal failure remains a challenging clinical condition, and effective options for patients that fail to achieve enteral autonomy are limited.
- Recent advances in the ability to culture intestinal stem cells and cellular components of the enteric nervous system have increased understanding of the regenerative capacity of the intestine.
- A tissue-engineered small intestine derived from cultured stem cells is attainable, although ongoing challenges exist.
Intestinal Failure

• IF is a clinical condition in which the body is incapable of supporting growth in children and/or maintenance fluids in adults due to a “reduction of functional gut mass” - needing of Parenteral Nutrition (PN) for at least 90 days


• Long-term PN is the mainstay of therapy


• Incidence of IF in a cohort of patients who developed surgical necrotizing enterocolitis (NEC) is 42%

Proposed Definition

Loss of bowel or enterocyte mass

- Surgical Resection
- Congenital Defect
- Disease associated loss of absorption

Obstruction
Dysmotility

Short Bowel Syndrome
Associated Intestinal Failure

O'Keefe et al, 2006
Epidemiology

• The prevalence of Intestinal failure is increasing

✓ Surgical short bowel syndrome: 7/1,000 live births for neonates with birth weight < 1500g
  – The incidence of NEC among very-low-birth-weight neonates increase by 3% for every 250 g decrement in birth weight below 1500g

✓ Prevalence of gastroschisis has increased to 49% - from 3.6 cases per 10,000 births (in 1995-2005 period) to 4.9 per 10,000 births (in the 2006-2012 period)
PIFCon (n=272)

- Necrotizing Enterocolitis (NEC): 26%
- Gastrochisis: 16%
- Intestinal atresia: 10%
- Volvulus: 9%
- Combination: 17%
- Aganglionosis: 4%
- Others: 18%

Morbidity and Mortality

- The common complications:
  - Intestinal Failure Associated Liver Disease (IFALD)
  - Sepsis from a Central Line Associated Bloodstream Infection (CLABSI's)

- IFALD and CLABSI’s are reduced in coordinated intestinal rehabilitation programs

- Cholestasis (direct bilirubin ≥ 2mg/dL), shorter bowel length, are risk factors for increased mortality, while care at a multidisciplinary intestinal rehabilitation program is protective

- Mortality ranges from 6.4% to 37.5% among reports from intestinal rehabilitation programs

Fullerton BS et al. J Peditr Surg 2016;51(1):96-100
Intestinal Rehabilitation

• Multidisciplinary therapy to manage IF in order to avoid, decrease or optimize TPN in an attempt to achieve enteral autonomy
  ✓ Dietary modifications
  ✓ Pharmacological interventions
  ✓ Avoiding PN complications: catheter related sepsis (CLABSI) and IFALD

• With the advances in Intestinal Rehabilitation, intestinal transplantation may NOT be required in some patients, survival on prolonged has become more common (>90%)

• With Intestinal Rehabilitation, enteral autonomy without transplant is even achievable for neonates with <20cm or less of small bowel

Goals: Intestinal Rehabilitation

✓ Avoidance of complications
✓ **Support normal growth and development**
✓ **Optimization and improvement of quality of life**
✓ Monitoring electrolytes status, minimizing the fecal loss of fluids and nutrients
✓ Wean from PN avoiding IFALD and CLABSIs
✓ Central goal is to achieve enteral autonomy
✓ Multiple strategies to promote bowel adaptation, optimizing enteral nutrition, treatment of bacterial overgrowth, early stoma closures and minimization of liver disease
✓ Improve long term survival for pediatric IF patients

Fullerton BS et al. Sem Pediatr Surg 2017;(26):328-335
Multidisciplinary Team

GI Pathology, GI Radiology, Ancillary support

- Peds Surgery
- Peds Gastro Nutrition Support
- Nurses specialized in Line care
- NICU Nurses & Neo
- Pharmacist
- Dieticians
- Social Work
- Speech & OT
- Child Psychology
Predictors to achieve enteral autonomy

Data from the Multicenter Pediatric Intestinal Failure Consortium (PIFCON) in 2015

- Longer residual small bowel
- Preservation of ileocecal valve
- Bowel in continuity
- Greater proportion on intact residual colon
- Lack of surgical lengthening procedures
- Younger age at time of intestinal loss
- Absence of severe liver disease
- Higher serum citrulline
- Diagnosis of NEC
- Care at an institution that does not offer intestinal transplantation (OR 6.56, 95% CI 2.53-16.98)

Ives GC et al. Small bowel Diameter in short bowel syndrome as a predictor factor for achieving enteral autonomy. J Pediatr 2016;178:275-277 e1
Predictors of Enteral Autonomy in Children with Intestinal Failure: A Multicenter Cohort Study

Faraz A. Khan, MD¹, Robert H. Squires, MD², Heather J. Litman, PhD¹, Jane Balint, MD³, Beth A. Carter, MD⁴, Jeremy G. Fisher, MD¹, Simon P. Horslen, MB, ChB⁵, Tom Jaksic, MD, PhD¹, Samuel Kocoshis, MD⁶, J. Andres Martinez, MD⁷, David Mercer, MD⁸, Susan Rhee, MD⁹, Jeffrey A. Rudolph, MD², Jason Soden, MD¹⁰, Debra Sudan, MD¹¹, Riccardo A. Superina, MD¹², Daniel H. Teitelbaum, MD¹³, Robert Venick, MD¹⁴, Paul W. Wales, MD, MSc¹⁵, and Christopher Duggan, MD, MPH¹, for Pediatric Intestinal Failure Consortium*

Objectives In a large cohort of children with intestinal failure (IF), we sought to determine the cumulative incidence of achieving enteral autonomy and identify patient and institutional characteristics associated with enteral autonomy.

Study design A multicenter, retrospective cohort analysis from the Pediatric Intestinal Failure Consortium was performed. IF was defined as severe congenital or acquired gastrointestinal diseases during infancy with dependence on parenteral nutrition (PN) >60 days. Enteral autonomy was defined as PN discontinuation >3 months.

Results A total of 272 infants were followed for a median (IQR) of 33.5 (16.2-51.5) months. Enteral autonomy was achieved in 118 (43%); 36 (13%) remained PN dependent and 118 (43%) patients died or underwent transplantation. Multivariable analysis identified necrotizing enterocolitis (NEC; OR 2.42, 95% CI 1.33-4.47), care at an IF site without an associated intestinal transplantation program (OR 2.73, 95% CI 1.56-4.78) and an intact ileocecal valve (OR 2.80, 95% CI 1.63-4.83) as independent risk factors for enteral autonomy. A second model (n = 144) that included only patients with intraoperatively measured residual small bowel length found NEC (OR 3.44, 95% CI 1.36-8.71), care at a nonintestinal transplantation center (OR 6.56, 95% CI 2.53-16.98) and residual small bowel length (OR 1.04 cm, 95% CI 1.02-1.06 cm) to be independently associated with enteral autonomy.

Conclusions A substantial proportion of infants with IF can achieve enteral autonomy. Underlying NEC, preserved ileocecal valve, and longer bowel length are associated with achieving enteral autonomy. It is likely that variations in institutional practices and referral patterns also affect outcomes in children with IF. (J Pediatr 2015;167:29-34).
The introduction of Hepatoprotective Strategies and Multidisciplinary Management has significantly improved the outcome of neonates with short bowel syndrome (SBS) who require parenteral nutrition (PN).
Long-term outcomes of pediatric intestinal failure

Brenna S. Fullerton, MD, Charles R. Hong, MD, Tom Jaksic, MD, PhD*

Department of Surgery, Center for Advanced Intestinal Rehabilitation, Boston Children’s Hospital and Harvard Medical School, 300 Longwood Avenue, Fegan 3, Boston, MA 02115

Table 1
Recent reported survival for children with severe intestinal failure cared for at intestinal rehabilitation programs.

<table>
<thead>
<tr>
<th>Reporting site: year published</th>
<th>N</th>
<th>Year of cohort</th>
<th>Inclusion criteria</th>
<th>Survival</th>
<th>Transplant-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston, USA: 2016</td>
<td>313</td>
<td>2002–2014</td>
<td>&gt; 90 days PN</td>
<td>94%</td>
<td>89%</td>
</tr>
<tr>
<td>Paris, France: 2016</td>
<td>217</td>
<td>2000–2013</td>
<td>&gt; 90 days PN, discharged on home PN</td>
<td>97%</td>
<td>91%</td>
</tr>
<tr>
<td>Helsinki, Finland: 2015</td>
<td>48</td>
<td>1988–2014</td>
<td>&gt; 90 days PN or SB length &lt; 25% predicted</td>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>Toronto, CA: 2015</td>
<td>33</td>
<td>2006–2009</td>
<td>Children assessed for intestinal transplant</td>
<td>76%</td>
<td>67%</td>
</tr>
<tr>
<td>PIFCON Multicenter: 2012</td>
<td>272</td>
<td>2000–2006</td>
<td>PN &gt; 60 days, initiated within 1st year of life</td>
<td>75%</td>
<td>57%</td>
</tr>
<tr>
<td>Ann Arbor, USA: 2011</td>
<td>60</td>
<td>2005–2009</td>
<td>&gt; 50% small bowel loss and &gt; 60 days PN</td>
<td>93%</td>
<td>93%</td>
</tr>
</tbody>
</table>
Patient selection for transplant evaluation in pediatric intestinal failure is predicted on the ability to assess long-term-free survival

- Data collected on patients from Feb 2002 and Sep 2014 by the Center for Advanced Intestinal Rehabilitation (CAIR), at Boston Children's Hospital
- 313 patients evaluated with pediatric IF as defined by the need for PN ≥ 90 days
- 126 patients who had liver biopsies (METAVIR F4) were included in the analysis of cirrhotic vs. noncirrhotic patients (all degrees of IFALD)

<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>One year and five year transplant-free survival and total survival rates.</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>All intestinal failure patients</td>
</tr>
<tr>
<td>N = 313</td>
</tr>
<tr>
<td>1 year transplant-free survival</td>
</tr>
<tr>
<td>5 year transplant-free survival</td>
</tr>
<tr>
<td>1 year survival</td>
</tr>
<tr>
<td>5 year survival</td>
</tr>
</tbody>
</table>

Percentages were derived from Kaplan-Meier curves for transplant-free survival and total survival. Data are reported as percentages.

* Only 126 patients with liver biopsy were included.
Intestine versus Multivisceral Transplant Survival Data

- Intestinal transplant is an option for patients experiencing complications of long-term PN who are expected to have a permanent intestinal failure, but outcomes are hindered by immunosuppression related complications

- As of 2015, the 5-year rate of patient survival was 75% for children receiving an isolated intestinal graft and 62% if both liver and intestine were transplanted


- A 25% reduction in the number of Intestinal Transplantation in the US was reported for the period from 2007 to 2012, probably as a result of the improved outcomes of intestinal rehabilitation

Intestinal Failure Associated Liver Disease

• IFALD can be referred as cholestasis or when the direct bili >2mg/dl

• Incidence ranges from 40-60% in children, even higher in premature neonates reaching 70%

• However, emerging data suggest efficiency in preventing IFALD and decrease in mortality

Buchman A et al. J Parenter Enteral Nutr 2002;26:S43-8
Goulet O. World Rev Nutr Diet 2015;112:90-114
NASPGHAN 2018

Florida Intestinal Rehabilitation Support and Treatment (FIRST) Program: Children FIRST: Description of Early Outcomes

Introduction

- The Salah Foundation Children’s Hospital, is the location of Children FIRST (Florida Intestinal Rehabilitation Support and Treatment), a multidisciplinary intestinal rehabilitation (MIR) program.
- The mainstay of modern medical therapy for intestinal failure (IF) is parenteral nutrition (PN).
- The overall goal of Children FIRST is to transition patients from parenteral to enteral nutrition (EN), in order to achieve enteral autonomy monitoring growth and development.
- The objective of this study is to describe early outcomes for patients undergoing IR at Children FIRST from July 2015 to October 2018.

Methods

- 13 patients with IF on PN were studied from July 2015 to March 2018. IF was defined as duration of PN >90 days.
- After IRB approval data collection started from July 2015 to March 2018 which included 13 patients. Ongoing data collection continued until October 2018 with a total of 18 IF patients.
- Medical records were reviewed retrospectively to determine gestational age, weight and length at birth. Age, weight, height and BMI z-scores were recorded in March 2018 and October 2018.
- Primary diagnosis, nutritional support data with EN and PN, liver panel and micronutrients were recorded retrospectively then prospectively. AST/ALT and bilirubin were analyzed for change over time since the initiation of care at FIRST for children.
- Electrolytes and liver panel were monitored at least once per month and micronutrients and trace elements were monitored approximately every 3 months and recorded for this study.
- Patients were closely followed at least weekly; nutritional assessment using WHO or Schofield equations with stress factors, were used to customize PN and caloric intake to optimize growth and development.

Results

- Table 1 shows demographics with female predominance, the average age of the patients during the data collection was 2.3 years old (median) with average weight z-score of -2.21 (mean), average height z-score of -2.41 (mean), and BMI z-score of 0.04 (mean). Table 2 shows the primary diagnosis. The average length of small bowel remaining after resection was 25.8 cm (range, 4 - 68 cm).
- Table 3 describes the nutrition support with average calories for PN and EN and macronutrients.
- Graph 1 & 2 show the average percent change in AST/ALT and bilirubin respectively, while receiving care at Children FIRST. Change was measured over an average length of 14.5 months.
- Of the 13 patients monitored up to March 2018, 92% (12) had at least one micronutrient deficiency and 30% (4) had ≥3 micronutrient deficiencies. Of the total 18 patients monitored up to October 2018, 83% (15) had at least one micronutrient deficiency and 22% (4) had ≥3 micronutrient deficiencies. The most common micronutrient deficiencies observed in order of frequency were vitamin D, copper, vitamin A, selenium and zinc.
- While undergoing IR at Children FIRST, there was 0% progression to cholestasis and 0% mortality rate with 25% (3) of the 13 patients achieving enteral autonomy. By October 2018, 28% (5) of the 18 patients had achieved enteral autonomy. The mean duration of PN for these 5 patients was 3.8 years (range: 0.9-8.2). Of these 5 patients, 2 had received referral for intestinal/multi-visceral transplant prior to presenting for a 2nd opinion. These 2 patients were weaned from PN at 1.1 and 7.4 years respectively.

Discussion

- IF includes a host of related disorders, with a number of patients having multiple diagnoses and extensive surgical histories affecting their growth and development.
- Common causes of death seen in patients with IF include intestinal failure associated liver disease and sepsis from central line associated blood stream infections. Achievement of enteral autonomy eliminates these risks.
- The best predictor to achieve enteral autonomy is bowel length; however several other factors play a role, especially care at a non-transplant intestinal rehabilitation center (OR 6.56)*.
- Studies have demonstrated that patients transitioning off PN have an increased risk of developing at least one micronutrient deficiency, however our data suggests that children are also at high risk for development of these deficiencies even while receiving full PN. The most common micronutrient deficiencies observed in our study were vitamin D, copper, followed by, vitamin A, selenium and zinc.
- Of the 18 patients currently undergoing IR, 67% (12) presented for a 2nd opinion where 58% (7) of patients who came for 2nd opinion were referred for intestinal/multi-visceral transplant.
- By using a multidisciplinary approach for IR with close physician monitoring during PN, patients achieved a 0% progression to cholestasis, 0% mortality rate and 25% achievement of enteral autonomy by March 2018 and 28% by October 2018.
- Our preliminary outcomes support that close monitoring of IF patients is important to: (1) identify and correct micronutrient deficiencies throughout the duration of PN and also during the weaning period (2) support the achievement of enteral autonomy regardless of the duration of PN dependency.
- Our study shows that a high percentage (58%) of patients referred for 2nd opinion who were previously referred for intestinal transplant can be successfully managed with IR and have the ability to achieve enteral autonomy. Therefore this demonstrates the importance of seeking a 2nd opinion at a non-transplant MIR center.

References:
New “Era” Strategies Treat/Prevent IFALD

- Prevention of Catheter Sepsis
- Manipulation of Microbioma
- Intestinal Rehab
  Multi-disciplinary Team Approach
- Lipid (≤1 g/kg/d) Limitation & Modification (SMOF & Fish oil)
- Cycling PN & Customized Nutrition Assessment
- Promote Motility by Optimizing Enteral Nutrition
- Stimulate Intestinal Adaptation and Hormonal Modulation

Intestinal Rehab
Multi-disciplinary Team Approach
Connection where thin meets thick part of the catheter is secured

Skinny part of catheter exposed from main dressing

Connection where thin meets thick part of the catheter should be underneath the main dressing. Most common area for breaks!

Broviac Central Line Dressing
Fish oil 1g/kg/day results in resolution of cholestasis in 50-75% of patients, decreased mortality, and reduce need for transplantation.

Soy, olive, fish and medium-chain oils (SMOFlipid, Fresenius Kabi) was approved in adults by the FDA in 2016.
Introduction

- Intestinal failure-associated liver disease (IFALD) can be the cause of increased morbidity and mortality in patients with intestinal failure (IF) \(^1\).
- The most common cause of IF in infants continues to be short bowel syndrome (SBS), of which the leading cause is necrotizing enterocolitis (NEC).
- Criteria for IFALD is a serum direct bilirubin level >2 mg/dL or alanine aminotransferase (ALT) >2 times the upper limit of normal after parenteral nutrition (PN) exposure for ≥14 days and no concurrent positive blood cultures to explain abnormal results \(^2\).
- The Salah Foundation Children's Hospital (SFCH) is the location of Children FIRST (Florida Intestinal Rehabilitation Support and Treatment), an intestinal rehabilitation program with the goal of optimizing and/or transitioning patients from parenteral to enteral nutrition (EN), in order to achieve enteral autonomy while providing a good quality of life.

Case Presentation

- The patient was a male infant born at 25 weeks gestation with a birthweight of 1,030 kg. Born and treated until he was 3 months of life in a primary facility.
- He developed NEC at 2 weeks of life requiring small bowel resection that resulted in 6 cm of remaining small bowel and no presence of ileoceleal valve.
- He was started on total parenteral nutrition (TPN) initially due to prematurity with soy lipids at an average of 2.2 g/kg/day for 24 hours. Consequently he developed SBS and continued TPN with soy lipid receiving at a max dose of 3.13 g/kg for the first 5 weeks of life during 24 hours.
- In an attempt to alleviate the patient’s IFALD, he was transitioned to SMOF and received an average of 2.17 g/kg/day for 2 months, max dose of 3.15 g/kg/day during 24 hours.
- Figure 1 shows patient’s direct bilirubin values while at the primary facility

Figure 1

Discussion

- This case demonstrates complete normalization of direct bilirubin with SMOF lipid while undergoing Intestinal Rehabilitation at FIRST Program at SFCH.
- One factor that is believed to have contributed to this patient’s cholestasis includes excessive lipid content, which is known to result in deregulation of hepatic lipid metabolism and to promote cholestasis \(^3\).
- This patient received excessive dosages of both soy and SMOF lipid emulsions when considering that reduced dosages of soy intravenous lipid emulsions of 1 g/kg may be protective against IFALD \(^3\).
- SMOF may be beneficial in the treatment and prevention of IFALD since it is rich in omega-3 polyunsaturated fatty acids (PUFAs), which lead to the production of anti-inflammatory derivatives. In addition, it is rich in α-tocopherol, an antioxidant that works to scavenge free radicals that result from the peroxidation of lipids \(^4\).
- SMOF use is not well described in pediatric cases or as an agent utilized to treat and reverse cases of IFALD.
- This case reinforces the importance of IF patients receiving care at an Intestinal Rehabilitation center in order to minimize risk of complications such as IFALD and thereby reducing risk of mortality and avoiding referrals to transplant centers.
- Prospective, randomized control studies are needed to substantiate the use of SMOF in the prevention and treatment of IFALD in the pediatric population.
- Since the cholestasis resolved in this patient, the dosage of SMOF was customized to provide 30% of calories from fat on his TPN. Now almost 10 months later, the patient is starting to be weaned off of TPN and is currently at 12 hours a day, growing and tolerating oral and enteral feeds well with no signs of liver disease.

Introduction

SMOF? (SMOF) is a unique combination of soybean oil (30%), olive oil (25%), medium chain triglycerides (30%), and fish oil (15%) intended for prevention of cholestasis in adults on total parenteral nutrition (TPN) but its usage is not well described in pediatric patients in the USA.

The objective of this study is to describe the trends of liver profile, micronutrients, nutritional data, and growth for pediatric intestinal failure (IF) patients undergoing Intestinal Rehabilitation (IR) at FIRST while using SMOF with the goal of providing up to 30% of calories of TPN from lipids.

Methodology

• After IRB approval, 14 pediatric patients with IF (duration of TPN = 90 days) with a mean age of 3.6 years (range: 4.6 months-14 years) were reviewed retrospectively from July 2015 to May 2019.
• The following data was reviewed after initiation of SMOF: recorded: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBil), direct bilirubin (DBil) nutritional support regimen, growth in 2 scores (WI, WHtR, and BMI), triene:tetraene ratio (TTR), micronutrients (Vitamins A, D, E, folate and B12), and trace elements (Zinc, Copper and Selenium).
• Patients were seen anywhere from 2-6 weeks and nutritional assessment using WHO or Scholfield equations were applied according to their age. Stress factor (1.7 for catch up growth) was used to customize their TPN regimen and caloric intake to optimize their growth.
• CDC’s WHO growth curve was used for those <2 years of age, and CDC’s growth curve was used for those ≥2 years of age.
• Micronutrients, trace elements and TTR were monitored every 3 months.
• Statistical analysis was performed using the two sample t-test with the power (p) set at ≥0.08.

Results

Table 1. Patient Demographics and Diagnosis

<table>
<thead>
<tr>
<th>Demographics</th>
<th>May 2019 14 patients</th>
<th>Primary diagnosis (N)</th>
<th>May 2019 14 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N, female: male)</td>
<td>14 (9F, 5M)</td>
<td>Necrotizing Enterocolitis</td>
<td>4</td>
</tr>
<tr>
<td>Age (mean; years)</td>
<td>3.8 (range: 4.6 months-14)</td>
<td>Jejunal Atresia</td>
<td>2</td>
</tr>
<tr>
<td>Gestational age (mean; weeks)</td>
<td>35 (range: 25-39)</td>
<td>Tutting Enteropathy</td>
<td>1</td>
</tr>
<tr>
<td>Birth weight (wt) (mean; grams)</td>
<td>2205 (range: 800-3380)</td>
<td>Duodenal Atresia</td>
<td>1</td>
</tr>
<tr>
<td>Birth length (mean; cm)</td>
<td>44 (range: 31-51)</td>
<td>Gastroesophageal Reflux Disease</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2. Patient Growth

| Weight (WI) Z score <2 YOA (mean) | -1.6 (range: -4.40-5.0) | 0.6 (range: -2.1-0.4) | +70% |
| Height (Ht) Z score >2 YOA (mean) | -1.3 (range: -2.4-0.7) | -0.9 (range: -2.5-0.1) | +31% |
| WHtR Z score >2 YOA (mean) | -1.2 (range: -3.2-0.12) | -1.1 (range: -2.5-1.6) | +8% |
| WHtR >2 YOA (mean) | -2.7 (range: -3.4-2.2) | -1.6 (range: -3.3-0.1) | +41% |
| Body Mass Index (BMI) Z score (mean) | -0.64 (range: -0.27-1.6) | -0.1 (range: -1.8-0.94) | -115% |

Table 3. Nutritional Support

| Total time on TPN (mean; months) | 31 (range: 2-170) | 46 (range: 9-174) |
| Total time on SMOF (mean; months) | 12.6 (range: 2-27) | |
| Days per week on TPN (mean; weeks) | 7 (range: 7) | 6.6 (range: 4-7) |
| Total TPN calories (mean; kcal/day) | 200 (range: 800-358) | 2205 (range: 800-3380) |
| Glucose (mean; g/day) | 102 (range: 45-220) | 104 (range: 30-185) |
| Glucose Infusion rate (mean; mg/kg/min) | 12 (range: 6-17) | 10.4 (range: 5-13) |
| Protein (mean; g/day) | 3.2 (range: 1.5-4.5) | 2.6 (range: 1.2-3.3) |
| Lipids (mean; g/kg/day) | 1.8 (range: 1-2.5) | 1.7 (range: 1-2.5) |
| Percent of TPN calories received from SMOF (mean; %) | 22% (range: 12-35) | 30% (range: 24-38) |
| Percent of total nutrition received from EN (mean; %) | 90% (range: 64%–189%) | 60% (range: 27%-76%) |

Discussion

• The evidence of this study demonstrates multiple benefits of SMOF for pediatric IF patients at FIRST.
• There were statistically significant improvements of ALT, AST, and Tbil. TTR remained normal in our patients despite the study.
• Intestinal failure associated liver disease (IFALD) is a known complication of long-term TPN in patients with IF and was not seen in this study possibly due to the blend of fatty acids in SMOF, enabling us to gradually reduce GIR and reduce overall hours on TPN per day while closely monitoring our patients at FIRST.
• SMOF has a ratio of 1:7 of fatty acids of 2:5:1, which reduces the hepatic cytokines that contributes to IFALD most notably TNF-a. It also has higher a-linolenic levels which have antioxidant and thereby anti-inflammatory effects.
• No patient progressed to cholestasis and there was 0% mortality supporting use of SMOF to avoid IFALD.
• The low hepatotoxicity of SMOF allows us to increase the kcals from lipids to reach the recommended dietary intake of up to 30% calories of TPN from fat, decreasing the dependence of kcals from glucose and decreasing GIR.
• This balanced physiologic blend of nutrition allows us to increase the concentration of triene acid in SMOF, enabling us to gradually reduce GIR and reduce overall hours on TPN per day while closely monitoring our patients at FIRST.
• SMOF has a ratio of 1:7 of fatty acids of 2:5:1, which reduces the hepatic cytokines that contributes to IFALD most notably TNF-a. It also has higher a-linolenic levels which have antioxidant and thereby anti-inflammatory effects.
• No patient progressed to cholestasis and there was 0% mortality supporting use of SMOF to avoid IFALD.
• The low hepatotoxicity of SMOF allows us to increase the kcals from lipids to reach the recommended dietary intake of up to 30% calories of TPN from fat, decreasing the dependence of kcals from glucose and decreasing GIR.
• This balanced physiologic blend of nutrition allows us to increase the concentration of triene acid in SMOF, enabling us to gradually reduce GIR and reduce overall hours on TPN per day while closely monitoring our patients at FIRST.
• SMOF has a ratio of 1:7 of fatty acids of 2:5:1, which reduces the hepatic cytokines that contributes to IFALD most notably TNF-a. It also has higher a-linolenic levels which have antioxidant and thereby anti-inflammatory effects.
• No patient progressed to cholestasis and there was 0% mortality supporting use of SMOF to avoid IFALD.
• The low hepatotoxicity of SMOF allows us to increase the kcals from lipids to reach the recommended dietary intake of up to 30% calories of TPN from fat, decreasing the dependence of kcals from glucose and decreasing GIR.
• This balanced physiologic blend of nutrition allows us to increase the concentration of triene acid in SMOF, enabling us to gradually reduce GIR and reduce overall hours on TPN per day while closely monitoring our patients at FIRST.
• SMOF has a ratio of 1:7 of fatty acids of 2:5:1, which reduces the hepatic cytokines that contributes to IFALD most notably TNF-a. It also has higher a-linolenic levels which have antioxidant and thereby anti-inflammatory effects.
• No patient progressed to cholestasis and there was 0% mortality supporting use of SMOF to avoid IFALD.
Most efficacious treatment IFALD
Enteral Nutrition

Hepatic Injury

X
Most Important Strategy: Enteral Nutrition

- Enteral Nutrients
  - Fuel for enterocytes – stimulating hyperplasia
  - Promote peristalsis – decreases bacteria overgrowth
  - Stimulate flow of gastrointestinal secretions and secretion of humoral factors
  - Stimulate oral secretions and oral function
Stimulate Bowel Adaptation

- **Luminals factors**: nutrients and secretions
  - pancreatic
  - biliary
- **Local factors**: prostaglandines and polyamines
- **Hormones and Peptides**
  
  Gastroenterology 2006;130:S117–S121

✓ **Organoid models and/or intestinal stem cell lines**
  
  Leushacke M at al. Gut. 2014

### Partial Listing of Some of the More Established Humoral Factors That Promote Intestinal Adaptation

- Mucosal-derived humoral factors
  - **Glucagon-like peptide 2 (GLP-2)**
  - Keratinocyte growth factor
  - Heparin-binding epidermal growth factor-like growth factor
  - Cytokines: TGF-a, IL-3, IL-11, and IL-15
  - Gut peptides: Neurotensin; Peptide YY; Bombesin
  - Insulin-like growth factor I and II (as well as distally expressed)
- Distantly-derived humoral factors
  - Epidermal growth factor (as well as locally in mucosal gland cells)
  - Human growth hormone (Somatropin)
  - Hepatocyte growth factor
  - Leptin
  - Gastrin

** Jeppesen PB et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology 2012; 143:1473–81**
Bacterial overgrowth – “Microbiota Dysbiosis”

- GI symptoms nonspecific clinic scenarios
  - Failure to thrive in children
- Malabsorption causing steatorrhea
  - Carbohydrate, Vit B12, fat-soluble vitamins, iron
- Vitamin excess: Folate
- Difficulty weaning from parenteral nutrition
- Gross and histologic bowel inflammation
  - Gastrointestinal bleeding; ulcers
- Bacterial translocation and endotoxemia
  - Endogenous sepsis/central line infections
  - Liver injury
- D-Lactic acidosis

1 Piper HG et al. JPEN 2016
2 Lilija HE et al. Microbiome 2015
3 Lee et al. J Pediatr 2015
Case Report

Multiple Micronutrient Deficiencies in a Child With Short Bowel Syndrome and Normal Somatic Growth

*Debora Duro, †Tom Jaksic, and *Christopher Duggan

*Division of Gastroenterology and Nutrition and †Department of Surgery and Center for Advanced Intestinal Rehabilitation, Children’s Hospital Boston, MA

- Close monitoring (vitamin and minerals) with supplementation is critical aspect of nutrition therapy during intestinal rehabilitation
- Common nutrient deficiencies (Vit D, Zn, Iron and B12) even with the use of full TPN and specially during weaning phase
- Trace elements in shortage; iodine deficiency; copper in cholestasis
- Refractory anemia: zinc and copper or anastomotic ulcers

Taking a STEP back: Assessing the outcomes of multiple STEP procedures

Meredith Barrett a, *, Farokh R. Demehri a, Graham C. Ives a, Kristen Schaedig b, Meghan A. Arnold a, Daniel H. Teitelbaum a

a Division of Pediatric Surgery, C.S. Mott Children's Hospital, University of Michigan; Ann Arbor, MI
b University of Michigan Clinical Financial Planning and Analysis Center, University of Michigan Health System; Ann Arbor, MI

Abstract

Purpose: Short bowel syndrome (SBS) is a highly morbid condition primarily because of parenteral nutrition (PN)-associated complications. Bowel lengthening via serial transverse enteroplasty (STEP) has become standard of care. While initial STEP have resulted in weaning from PN, outcomes of repeated STEP (ReSTEP) are not well described. We investigated outcomes of initial STEP compared to ReSTEP procedures.

Methods: This retrospective review of STEP included 17 children and a total of 24 procedures. Demographics, complications, hospital readmission rates, postoperative costs, and PN weaning were analyzed.

Results: Neither patient-specific data nor the etiology of SBS was predictive of requiring a ReSTEP. PN weaning was more likely in the year following a first STEP (18% wean rate vs. 0% for ReSTEP, \( p > .05 \)). No ReSTEP patients reached enteral autonomy. Enteral nutrition (%EN) increases were greater after first STEP compared to ReSTEP (26.0% vs. 4.7%, \( p = 0.03 \)). This trend was true for bowel length as well, where first STEP resulted in a 51% increase in bowel length compared to a 20% increase after in ReSTEP (\( p = 0.02 \)).

Conclusions: ReSTEP failed to result in significant PN weaning, with no ReSTEP patients achieving enteral autonomy during follow-up. Given its higher costs, smaller bowel length gains, and limited ability to produce enteral autonomy, surgeons should carefully consider performing ReSTEP procedures.

Level of evidence: Level III.
Future Directions...

Concise Review: The Potential Use of Intestinal Stem Cells to Treat Patients with Intestinal Failure

Sung Noh Hong, a,b James C.Y. Dunn, a Matthias Stelzner, c,d Martin G. Martin a

Key Words: Intestinal failure • Congenital diarrhea • Microvillus inclusion disease • Congenital tufting enteropathy • Intestinal stem cell

ABSTRACT

Intestinal failure is a rare life-threatening condition that results in the inability to maintain normal growth and hydration status by enteral nutrition alone. Although parenteral nutrition and oral or organ allotransplantation have improved the survival of these patients, current therapies are associated with a high risk for morbidity and mortality. Development of methods to propagate adult human intestinal stem cells (ISCs) and pluripotent stem cells raises the possibility of using stem cell-based therapy for patients with monogenic and polygenic forms of intestinal failure. Organoids have demonstrated the capacity to proliferate indeﬁnitely and differentiate into the various cellular lineages of the gut. Genome-editing techniques, including the overexpression of the corrected form of the defective gene, or the use of CRISPR clustered regularly interspaced short palindromic repeats/Cas9 to selectively correct the monogenic disease-causing variant within the stem cell, make autologous ISC transplantation a feasible approach. However, numerous techniques still need to be further optimized, including more robust ex vivo ISC expansion, native ISC ablation, and engraftment protocols. Large-animal models can be used to develop such techniques and protocols and to establish the safety of autologous ISC transplantation because outcomes in such models can be extrapolated more readily to humans. STEM CELLS TRANSLATIONAL MEDICINE 2017;6:666–676

New approaches to increase intestinal length: Methods used for intestinal regeneration and bioengineering

Ali Shirafkan, Mauro Montalbano, Joshua McGuire, Cristiano Rastellini, Luca Cicalèse
“FIRST” Family Support Group for Families with Children with Intestinal Failure

THANK YOU!!!