Short Bowel Syndrome: Breaking Frontiers to Intestinal Regeneration

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Survival Curves for Each 5 Year Period of Care

Cumulative Survival

Days Post-Onset of Intestinal Failure

Hess, et al

93.3% Survival

70.6% Survival
Primary Outcomes: Enteral Autonomy, Death, and Transplantation

PIFCON 2011 - but most data from 2000-2003

**Primary Outcomes:**

- Enteral Autonomy
- Death
- Transplantation

<table>
<thead>
<tr>
<th>Number at risk for</th>
<th>0 mo</th>
<th>12 mo</th>
<th>24 mo</th>
<th>36 mo</th>
<th>48 mo</th>
<th>60 mo</th>
<th>72 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>272</td>
<td>220</td>
<td>182</td>
<td>126</td>
<td>126</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Transplantation</td>
<td>272</td>
<td>199</td>
<td>142</td>
<td>89</td>
<td>52</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>Enteral autonomy</td>
<td>272</td>
<td>120</td>
<td>42</td>
<td>26</td>
<td>14</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>
Think of intestinal engineering = Construction Project
Think of longitudinal bowel lengthening like a room divider!
Intestinal lengthening

- Intestinal lengthening surgery
- Advanced by Professor Bianchi in Manchester
- Splits the mesentary – and then longitudinally divides the bowel
- Can double bowel length
Serial Transverse Enteroplasty (STEP)
What are current and future strategies to approach our patients with intestinal failure?
Major Reconstruction approaches
Extending or Lengthening original!
Traditional Treatment Methods:
• Total Parenteral Nutrition – possible liver disease, catheter sepsis
• Growth Hormones – growth reversal once stopped, uncontrolled growth (malignancy), unproven
• Surgical Lengthening – possible leakage, requires pre-dilated bowel. Up to 45% failure.
• Transplant – Costly, requires long-term immunosuppressant medication, risk of infection, 50% rejection at five years.

Promising New Method: Mechanotransduction
• Translation from mechanical stimulus to biochemical signal (growth)
• Experiments with animals and patients have shown permanent growth of functional tissue.
Isolated Bowel Segments

CONTROL SEGMENT

Remaining bowel returned to continuity

Drain

Infusion catheter

STUDY SEGMENT
Results: 1:2.7 fold
Will bowel remain lengthened?

Experimental design

Motility

Length and Function

Koga, et al
Ann Surg
Visual evidence of new vessel growth

Implant

Harvest
Concept of a clinical implantation of an enterogenesis device
Completely implantable device via Gastrostomy site
Current Experiment, Implantation Notes

Linear Hydraulic Device

- Balloons were made with Foley catheters and are independently inflated with air (max 10cc each)
- Device retracts fully with syringe is pulled back
- Device expands fully with approximately 1.25 cc of water injection
- Dimensions
  - Retracted balloon to balloon length is approximately 5.5 cm
  - Device extends approximately 4.0 centimeters (0.7X)

Implantation Notes

- Initial measurements shown in photo
- Device repair was needed during implant

[Diagram of Linear Hydraulic Device with Balloons]

26 fr Foley, 5cc Balloons

[Implant Photo]

Ann Arbor, MI 48109
Current Experiment, Implantation Notes

After 7 days of cycled extension:

- Distracted segment: $67\pm15\%$ increase in length versus fed, non-distracted bowel,
- Absolute gain of $12.9 \pm 7.6$ cm.
- Epithelial cell proliferation vs. control: $53.4 \pm 4.4\%$ vs $41.0 \pm 2.5\%$; $p = 0.04$

One issue is balloon slippage
Current Experiment, Implantation Notes

Linear Hydraulic Device

• Note latex balloon covered with a “Scruffy” pot scrubber and fenestrated latex bands
• Masked latex attachment successfully generated attachment strength @ inflation (>500 gf) with detachment upon deflation (80 gf).
• 7 days: Distracted segment 45.6% vs non-lengthened, adjacent unfed bowel, corresponding to an absolute gain of 7 cm.

Next Step
• Refinement for IDE
• Application to FDA
• Clinical trial
Reconstruction approaches with a disaster

Burn it down!

JUST

REMODELING MY HOUSE
What if there is no intestine to elongate?

*Intestinal volvulus*
Start reconstruction with a Foundation
Decellularization – Porcine SB

4 hours PBS

0.1% Triton X-100 24 hrs

3 hours DNAs

4% Na Deoxycholate

4 hours
Reconstitution of decellularized intestinal extracellular matrix

7 days

Inducible Human organoid

Courtesy of Spence Lab
Confirmation of decellularization

Re-seed with human intestinal organoids

Regrow in tissue generator
Decellularized Porcine Intestine
Supported by NIH-R01 AI-44076-12

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No Disclosures
Thank you

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Growth Factors for SBS
Like pouring more concrete
GLP-2: from distal bowel – and acts only on small bowel
### Teduglutide: STEPS-2 (Extension Study) PS Volume Reductions—Completers*

<table>
<thead>
<tr>
<th>With teduglutide treatment:</th>
<th>TED/TED†</th>
<th>PBO/TED</th>
<th>NT/TED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=30</td>
<td>n=29</td>
<td>n=6</td>
</tr>
<tr>
<td>PS requirement at baseline‡, L/week</td>
<td>12.4</td>
<td>10.4</td>
<td>12.8</td>
</tr>
<tr>
<td>Clinical response (20%–100% PS volume reduction), n (%)</td>
<td>28 (93)</td>
<td>16 (55)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>PS volume reduction from baseline‡, mean L/week (%)</td>
<td>7.6 (66)</td>
<td>3.1 (28)</td>
<td>4.0 (39)</td>
</tr>
<tr>
<td>PS volume requirement at 24 months in STEPS-2, mean L/week</td>
<td>4.9</td>
<td>7.3</td>
<td>8.8</td>
</tr>
</tbody>
</table>

NT/TED=no treatment in STEPS; PS=parenteral support (parenteral nutrition and/or intravenous fluids); PBO/TED=randomized to placebo in STEPS; TED=teduglutide; TED/TED=randomized to TED in STEPS

*65/88 patients who completed the 24-month study
†TED/TED group received a total of 30 months of TED during STEPS and STEPS-2
‡Baseline was start of TED treatment: at randomization in STEPS for TED/TED patients; at start of STEPS-2 for PBO/TED and NT/TED patients

### Teduglutide: STEPS-2 (Extension Study) Most Common AEs—GI*

<table>
<thead>
<tr>
<th>Condition</th>
<th>All Patients, N=88† n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>30 (34)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (19)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>14 (16)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (15)</td>
</tr>
<tr>
<td>GI stoma‡ complications</td>
<td>12 (33)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (10)</td>
</tr>
</tbody>
</table>

AE=adverse event; GI=gastrointestinal

*Reported in ≥10% of all patients
†Intent-to-treat population
‡Among patients with stoma (n=36)

# Report of 111 Consecutive Patients Enrolled in the International Serial Transverse Enteroplasty (STEP) Data Registry: A Retrospective Observational Study

Brian A Jones, MD, Melissa A Hull, MD, Kristina M Potanos, MD, David Zurakowski, PhD, Shimaee C Fitzgibbons, MD, Y Avery Ching, MD, Christopher Duggan, MD, MPH, Tom Jaksic, MD, PhD, FACS, Heung Bae Kim, MD, FACS, on behalf of the International STEP Data Registry

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death/transplant (n = 16)</th>
<th>Survival (n = 81)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory values at STEP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, mg/dL, median (IQR) (n = 73)</td>
<td>9.0 (2.0−15.3)</td>
<td>1.9 (0.5−8.0)</td>
<td>0.00</td>
</tr>
<tr>
<td>Direct bilirubin, mg/dL, median (IQR) (n = 59)</td>
<td>7.3 (1.6−9.5)</td>
<td>1.2 (0.1−5.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>INR, mean ± SD (n = 50)</td>
<td>1.15 ± 0.19</td>
<td>1.17 ± 0.21</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Operative data, cm, median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-STEP bowel length (n = 92)</td>
<td>30 (18−40)</td>
<td><strong>49 (28−85)</strong></td>
<td>0.01</td>
</tr>
<tr>
<td>Pre-STEP bowel width (n = 80)</td>
<td>4.0 (3.8−6.0)</td>
<td>5.3 (4.0−7.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Post-STEP bowel length (n = 81)</td>
<td>52 (34−77)</td>
<td><strong>75 (49−117)</strong></td>
<td>0.02</td>
</tr>
<tr>
<td>Post-STEP bowel width (n = 84)</td>
<td>1.8 (1.0−2.0)</td>
<td>2.0 (1.5−2.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Staple firings (n = 94)</td>
<td>9 (5−13)</td>
<td>10 (7−17)</td>
<td>0.10</td>
</tr>
<tr>
<td>Presence of ileocecal valve, n (%) (n = 95)</td>
<td>5 (31)</td>
<td>25 (32)</td>
<td>0.99</td>
</tr>
</tbody>
</table>