From the cradle to enteral autonomy: Infant with 10 cm bowel: is there hope?

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Case Scenario

- Baby born at 26 weeks gestation with birth weight of 1200 grams, result of IVF.
- Initially required ventilatory and ionotropich support.
- Cranial USG with grade I bilateral intraventricular hemorrhage.
- Day 15: oral feeds introduced.
- Day 17: distended abdomen with high NG residuals. AXR with pneumatosis and portal venous air.
Case Scenario

► OR: most of the small bowel necrotic except for proximal 10 cm. Colon necrotic to mid transverse colon.

► Situation d/w parents: Mother wants everything, father wants to withdraw care.

► What do u do?
What defines short bowel syndrome?

- A multisystemic disorder and need for prolonged parenteral nutrition caused by inadequate length of small bowel usually less than half the expected for gestational age.

Etiology

- Mid-gut volvulus
- Intestinal atresia
- Necrotizing enterocolitis
- Crohn’s disease
  - Multiple resections
- Vascular insult
- Radiation enteritis
- Trauma
- Malignancy
- Obstruction

Historically leading cause of short bowel syndrome

Soden JS, Sem Ped Surg 2010;19:10-19
Presentation of SBS

► Altered bowel anatomy related:
  - Chronic diarrhea
  - Malabsorption
  - Fluid/electrolyte disturbances
  - Micronutrient deficiency
  - Oxalate nephropathy
  - Bacterial overgrowth
  - D lactic acidosis
  - Renal dysfunction
  - Metabolic bone disease
  - Peptic ulcer disease

► Central line related
  - Infection
  - Occlusion
  - Breakage
  - Central vein thrombosis

► PN related
  - Hepatic
  - Biliary
Intestinal adaptation

► Acute phase

- Starts immediately after bowel resection and lasts 1-3 months
- High ostomy output or severe diarrhea
- Life-threatening dehydration and electrolyte imbalances
- Extremely poor absorption of all nutrients
- Development of hypergastrinemia and hyperbilirubinemia
- Most require PN support

Sundaram et al, J Clin Gastroenterol, 2002
Intestinal adaptation

- Adaptation phase
  - Begins within 48 hours of resection and lasts up to 1-2 years
  - Approximately 90% of the bowel adaptation takes place during this phase.
  - Enterocyte hyperplasia, villous hyperplasia, and increased crypt depth occur, resulting in increased surface area. Intestinal dilatation and lengthening also occur.
  - Luminal nutrition is essential for adaptation and should be initiated as early as possible. Parenteral nutrition is also essential throughout this period.

Sundaram et al, J Clin Gastroenterol, 2002
Intestinal adaptation

- Maintenance phase
  - The absorptive capacity of the intestine is at its maximum.
  - Nutritional and metabolic homeostasis can be achieved by oral feeding, or patients are committed to receiving supplemental or complete nutritional support for life.

Sundaram et al, J Clin Gastroenterol, 2002
Treatment goal in SBS

► ASSIST AND ACCELERATE INTESTINAL ADAPTATION
Treatment goals in SBS

- Prevent and correct nutritional deficiencies
- Maintain adequate nutrition and growth
- Prevent and correct dehydration, diarrhea
- Prevent and correct complications
- Improve quality of life
- Restore enteral autonomy
Treatment options in SBS

► Nutrient factors: PN/EN
  ▪ Fluids
  ▪ Medications
  ▪ Antimotility
  ▪ Antisecretory
  ▪ Bile acids
  ▪ Antibiotics
  ▪ Early enteral feeding
    (Complex diet better)

► Non nutrient factors

► Surgery
  ▪ Autologous GI reconstruction
  ▪ Transplantation
Problems with medical approaches

- PN still frequently necessary
- Costly
- Reduced quality of life
- Infant mortality with short gut remains high.

Average cost of PN is:
- $70,000-$390,000/child/yr
- ~10% reduction would equal a yearly savings of $140,000,000 to $780,000,000

How to weigh yourself and get the most accurate result. I can't believe I have been doing it wrong all these years!

We must get the word out!
Novel hormonal approaches

► Trophic factors:
  - Growth hormone, insulin-like growth factor-I
  - Glutamine, Epidermal growth factor
  - Neurotensin, bombesin, glucagon-like peptide 2 (GLP-2)
  - Leptin, steroids, thyroxine

O’Keefe et al. DDW abstract 2008
Surgery in SBS

► Prevention
  ▪ Smallest possible resection should be performed
  ▪ Second-look operations, to allow the ischemic bowel to demarcate

► Restore continuity
  ▪ Relieve obstruction
  ▪ Repair fistulae
  ▪ Recruit bypassed/unused bowel
Surgery in SBS

**Indicated when all else fails**: Choice of surgery therapy influenced by existing bowel length, function and caliber.

**Autologous GI reconstruction**
- *Delay intestinal transit time*
  - Construction of various valves and sphincters
  - Construction of antiperistaltic segments
- *Optimize function*
  - Intestinal tapering and imbrication
  - Bianchi intestinal lengthening procedure
  - STEP procedure
  - Kimura Iowa procedure

**Small bowel transplantation**
- Isolated small intestinal graft
- Combined liver/small intestinal grafts
The leaves of the mesentery are separated and a tunnel is created to separate the vasculature to alternate sides (A).

The linear stapler is passed through this tunnel and the bowel is divided longitudinally (B, C).

A lazy “s” is then formed to bring the open ends together and hand-sewn anastomosis is performed to restore continuity (D).
STEP procedure
“...while I was a medical student,.....He said it would never work," Dr. Kim said. "Being a student, I just sort of chalked it up as a stupid idea and forgot about it." ....idea came back to him 10 years later.... he sketched his plan for another surgeon, Dr. Tom Jaksic.
Bowel after the STEP procedure. Note the dotted line marking the antimesenteric border. This keeps the bowel from twisting during placement of the stapler.

The final result of the STEP is a zig zag-shaped channel of bowel that is longer and narrower than the original dilated loop.
The channel size is determined by the length of the staple line and the distance between staple lines. We try to keep the channel size constant along the length of the bowel.
Intestinal Transplantation

► Indications

- Used as salvage therapy in patients who fail autologous GI reconstruction.
- Irreversible liver failure with portal HTN with need for life long PN and complication of PN
- Prior to lengthening procedure.

► Options

- Isolated intestinal transplant
- Combined with liver transplant
- Multivisceral transplant
Bianchi et al

1999: survival rate 45%
The mean small bowel length was 30.6 ± 15.1 cm before LILT and 54.71 ± 26.95 cm after LILT.

Overall survival was 77.36%.

75.86% patients were completely weaned off PN and are completely free of central venous access.

The median weaning time was 10.4 months (1.5–60 months).
58% of the patients gained weight to a higher percentile.

Of the school-age patients, 75% attend a regular school, and only 25% are in a school for handicapped children. Two patients are already employed without restrictions.
Use of multisystemic approach and novel techniques:

- Hepatosparing TPN
- Bowel expansion
- Bowel lengthening
- Hormonal therapies
- Early introduction of enteral feeds
Overall survival: 92%
91% patients off TPN
Time to wean off TPN: 6 mo (2 weeks - 12 mo)

Bianchi et al, 2012

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age at LITT (months)</th>
<th>Length of residual gut (cm)</th>
<th>Length of gut pre-LITT (cm)</th>
<th>Length of gut post LITT (cm)</th>
<th>TPN status</th>
<th>Time on TPN post LITT</th>
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<tbody>
<tr>
<td>1</td>
<td>Atresia/Meconium ileus</td>
<td>126</td>
<td>-</td>
<td>140</td>
<td>260</td>
<td>Off</td>
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<td>2</td>
<td>Small bowel Atresia</td>
<td>22</td>
<td>25</td>
<td>43</td>
<td>83</td>
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<tr>
<td>3</td>
<td>Gastrochisis</td>
<td>129</td>
<td>-</td>
<td>110</td>
<td>210</td>
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<td>8</td>
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<td>-</td>
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<tr>
<td>5</td>
<td>Ganglioneuroma</td>
<td>108</td>
<td>25</td>
<td>25</td>
<td>45</td>
<td>LFU</td>
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<td>6</td>
<td>Hirschsprung’s</td>
<td>78</td>
<td>-</td>
<td>88</td>
<td>150</td>
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<td>N/A</td>
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<td>7</td>
<td>Gastrochisis/Atresia</td>
<td>9</td>
<td>25</td>
<td>35</td>
<td>65</td>
<td>LFU</td>
<td>N/A</td>
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<tr>
<td>8</td>
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<td>79</td>
<td>-</td>
<td>90</td>
<td>120</td>
<td>OFF</td>
<td>N/A</td>
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<td>9</td>
<td>Gastrochisis</td>
<td>13</td>
<td>35</td>
<td>85</td>
<td>125</td>
<td>OFF</td>
<td>N/A</td>
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<td>10</td>
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<td>13.8</td>
<td>-</td>
<td>125</td>
<td>220</td>
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<td>4</td>
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<td>11</td>
<td>Gastrochisis/Volvulus</td>
<td>41</td>
<td>-</td>
<td>30</td>
<td>60</td>
<td>ON</td>
<td>13.4</td>
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<td>12</td>
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<td>6.5</td>
<td>40</td>
<td>68</td>
<td>136</td>
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<td>13</td>
<td>Necrotizing enterocolitis</td>
<td>56.6</td>
<td>-</td>
<td>60</td>
<td>120</td>
<td>Died</td>
<td>-</td>
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<tr>
<td>14</td>
<td>Gastrochisis/Atresia</td>
<td>13.2</td>
<td>-</td>
<td>60</td>
<td>120</td>
<td>Off</td>
<td>6.5</td>
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<td>15</td>
<td>Gastrochisis</td>
<td>6</td>
<td>10</td>
<td>18</td>
<td>37</td>
<td>Off</td>
<td>11</td>
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<tr>
<td>16</td>
<td>Gastrochisis</td>
<td>6.4</td>
<td>30</td>
<td>60</td>
<td>90</td>
<td>Off</td>
<td>10</td>
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<td>17</td>
<td>Gastrochisis/Volvulus</td>
<td>28.8</td>
<td>25</td>
<td>40</td>
<td>80</td>
<td>Off</td>
<td>8</td>
</tr>
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<td>18</td>
<td>Small bowel Atresia</td>
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<td>20</td>
<td>20</td>
<td>40</td>
<td>Off</td>
<td>10</td>
</tr>
<tr>
<td>19</td>
<td>Gastrochisis/Atresia</td>
<td>48</td>
<td>-</td>
<td>25</td>
<td>45</td>
<td>ON</td>
<td>**</td>
</tr>
</tbody>
</table>

Med: 22
Med: 25cm
Med: 60
Med: 90
Med: 10
- Resulted in 69% increase in small intestinal length and three fold tapering of the intestinal diameter.
- Increase in mean enteral tolerance from 31% to 67% of total calories at median followup of 12.6 months, which resulted in 116% increase relative to pre-STEP baseline.
- 48% were completely weaned off TPN.
- Transplantation was required in 7.9%.
- Overall survival was 92.16%.

Figure 3. Graphic representation of the change in tolerance of enteral calories for 21 short bowel syndrome patients undergoing the serial transverse enteroplasty procedure, based on length of followup.
Autologous GI reconstruction: STEP Procedure

<table>
<thead>
<tr>
<th>Institution [Reference]</th>
<th>Number of Procedures</th>
<th>Children (%)</th>
<th>Success (%)</th>
<th>Mortality (%)</th>
<th>Transplant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEP Registry [23]</td>
<td>38</td>
<td>37 (97)</td>
<td>29 (76)</td>
<td>3 (8)</td>
<td>3 (8)</td>
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<tr>
<td>Omaha [18]</td>
<td>34</td>
<td>27 (79)</td>
<td>30 (88)</td>
<td>3 (9)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>64 (88)</td>
<td>59 (82)</td>
<td>6 (8)</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

Sudan et al, Adv Surg 2008
Number of patients receiving PN post-STEP

Wales et al, Jour of Pediatr Surg, 2007
<table>
<thead>
<tr>
<th></th>
<th>Bianchi (n=43)</th>
<th>STEP (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remnant SB length</td>
<td>44 (11-150)</td>
<td>45 (14-125)</td>
</tr>
<tr>
<td>Final Bowel Length</td>
<td>68 (20-160)</td>
<td>65 (23-150)</td>
</tr>
<tr>
<td>% Increase over original</td>
<td>48% (7-83)</td>
<td>52 (12-200)*</td>
</tr>
<tr>
<td>% Enteral calories initial</td>
<td>18 (0-100)</td>
<td>10 (0-100)</td>
</tr>
<tr>
<td>% Enteral calories 3 mos</td>
<td>50 (0-100)</td>
<td>65 (42-100)*</td>
</tr>
<tr>
<td>% Enteral calories 6 mos</td>
<td>70 (0-100)</td>
<td>93 (25-100)</td>
</tr>
<tr>
<td>Survival</td>
<td>88%</td>
<td>95%</td>
</tr>
</tbody>
</table>

69% patients completely weaned off TPN
Liver disease, when present, was reversed in 80%

After LILT, all patients with liver fibrosis who could be weaned from PN showed a normalization of liver enzymes and bilirubin within 12 months, independent of the grade of liver fibrosis preoperatively.

**Table 4** Results of liver biopsies classified according to Desmet et al. Patient 4 died perioperatively due to intractable gastrointestinal bleeding

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cause leading to short bowel syndrome</th>
<th>Period of parenteral nutrition in months</th>
<th>Inflammation</th>
<th>Fibrosis</th>
<th>Actual nutrition</th>
<th>ALAT/ASAT preoperative</th>
<th>ALAT/ASAT actual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>gastrochisis</td>
<td>38</td>
<td>0</td>
<td>0-1</td>
<td>external</td>
<td>77/68 U/l</td>
<td>23/41 U/l</td>
</tr>
<tr>
<td>2</td>
<td>gastrochisis</td>
<td>8</td>
<td>0-1</td>
<td>1-2</td>
<td>external</td>
<td>44/45 U/l</td>
<td>39/41 U/l</td>
</tr>
<tr>
<td>3</td>
<td>gastrochisis</td>
<td>30</td>
<td>1</td>
<td>1-2</td>
<td>partial parenteral</td>
<td>28/36 U/l</td>
<td>29/44 U/l</td>
</tr>
<tr>
<td>4</td>
<td>gastrochisis</td>
<td>33</td>
<td>2</td>
<td>3-4</td>
<td>parenteral</td>
<td>49/58 U/l</td>
<td>49/58 U/l</td>
</tr>
<tr>
<td>5</td>
<td>necrotting enterocolitis</td>
<td>8</td>
<td>1-2</td>
<td>2-3</td>
<td>external</td>
<td>147/207 U/l</td>
<td>33/27 U/l</td>
</tr>
<tr>
<td>6</td>
<td>necrotting enterocolitis</td>
<td>13</td>
<td>2</td>
<td>3-4</td>
<td>parenteral</td>
<td>320/395 U/l</td>
<td>380/410 U/l</td>
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<tr>
<td>7</td>
<td>necrotting enterocolitis</td>
<td>9</td>
<td>2</td>
<td>3-4</td>
<td>parenteral</td>
<td>62/66 U/l</td>
<td>24/29 U/l</td>
</tr>
<tr>
<td>8</td>
<td>atresia</td>
<td>14</td>
<td>0-1</td>
<td>0-1</td>
<td>external</td>
<td>54/44 U/l</td>
<td>22/24 U/l</td>
</tr>
<tr>
<td>9</td>
<td>atresia</td>
<td>6</td>
<td>0-1</td>
<td>0-1</td>
<td>external</td>
<td>74/76 U/l</td>
<td>23/28 U/l</td>
</tr>
<tr>
<td>10</td>
<td>situs inversus, apple peel syndrome</td>
<td>12</td>
<td>1</td>
<td>1-2</td>
<td>external</td>
<td>107/176 U/l</td>
<td>28/36 U/l</td>
</tr>
<tr>
<td>11</td>
<td>multiple atresias</td>
<td>39</td>
<td>0-1</td>
<td>2</td>
<td>external</td>
<td>13/32 U/l</td>
<td>29/38 U/l</td>
</tr>
<tr>
<td>12</td>
<td>atresia</td>
<td>8</td>
<td>1-2</td>
<td>3-4</td>
<td>parenteral</td>
<td>157/248 U/l</td>
<td>37/40 U/l</td>
</tr>
<tr>
<td>13</td>
<td>volvulus</td>
<td>12</td>
<td>0-1</td>
<td>0-1</td>
<td>partial parenteral</td>
<td>56/60 U/l</td>
<td>54/89 U/l</td>
</tr>
<tr>
<td>14</td>
<td>volvulus</td>
<td>32</td>
<td>1</td>
<td>2-3</td>
<td>partial parenteral</td>
<td>55/80 U/l</td>
<td>50/38 U/l</td>
</tr>
</tbody>
</table>
Overall and Graft Survival

**US**

- **1 year overall and graft survival**
  - Isolated bowel 89% and 79%
  - Liver and bowel 72% and 69%

- **10 year overall and graft survival**
  - Isolated bowel 46% and 29%
  - Liver and bowel 42% and 39%

Randomized, Controlled Trial of GLP-2 Analog in PN-dependent SBS

83 PN-dependent SBS patients

0-8 weeks
Optimize PN (0-8 wks)

4-8 weeks
Stabilize PN

24 weeks

Placebo (n=16)
6.3% PN ↓
31.3% AEs

Teduglutide 0.05 mg/kg/d (N=35)
*45.7% PN ↓
*LBM 632g ↑
*Citr +10.9 ↑
37.1% AEs

Teduglutide 0.1 mg/kg/d (N=32)

Results

Endpoints
1. PN reduction > 20% weekly needs b/w wks 20-24
2. Lean body mass
3. Plasma citrulline

O'Keefe et al. DDW abstract 2008
Role of Growth hormone + glutamine + diet

Recombinant Growth hormone + glutamine + diet: reduce patients’ need for TPN, even totally weaned off.

Role of Omegaven

- Potential to reverse liver disease in infants with SBS.
- More children with SBS achieve full enteral tolerance when switched to omegaven from standard soy based omega-6 lipid formulations.

Wales et al. Jour of Ped Gastroenterology and nutrition, 2009
Other Issues
Issues: Cost

Spencer et al, Am J Clin Nutr; 2008; 88: 1552-9
In 2006, the United States spent $2.1 trillion on health care.

Five percent of the population accounts for almost half (49 percent) of this total health care expenses.

The elderly (age 65 and over) made up around 13 percent of the U.S. population in 2002, but they consumed 36 percent of total U.S. personal health care expenses.

$4 billion spent for end stage elderly cancer patients in 2005.

The five most expensive health conditions were heart disease, cancer, trauma, mental disorders, and pulmonary conditions.

$376 billion: health expenditure on diabetes in 2010.
Neurodevelopmental outcomes
Neurodevelopmental outcomes

► Bianchi et al, 2012: Infants pre-surgery showed delayed milestones which were later achieved post-surgery. All the children in the series who are at school age are attending mainstream schools.

► Reinshagen et al, 2008: Of the school-age patients, 75% attend a regular school, and only 25% are in a school for handicapped children. Two patients are already employed without restrictions.
“It is not how long it is, but what you do with it, ….”
Anonymous, about 500 BC