New Treatments for SBS

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Overview

• Review of short bowel syndrome
• Gut adaptation
• Diet strategies
• New approaches
What is Short Bowel Syndrome (SBS)?

- No totally accepted definition
- Agreement that SBS exists when a patient’s remaining intestinal function cannot meet nutrient needs for survival, growth (children), hydration, electrolyte balance
What is Short Bowel Syndrome (SBS)?

• In adults, a substantial part of the bowel is removed by surgeons because of
  – Blood clots in the artery or vein that feed the bowel cause tissue death
  – Malrotation (volvulus)
  – Crohn’s disease causes blockages, ulcers
  – Trauma to the abdomen
  – Adhesions that cause bowel obstruction
  – Radiation damage from cancer treatment
What is Short Bowel Syndrome (SBS)?

- In children, a substantial part of the bowel is removed by surgeons because of:
  - Necrotizing enterocolitis in 35% (parts of the bowel die as a consequence of prematurity in very low birth weight newborns)
  - Atresia in 20% (narrowing or absence of a segment of bowel)
  - Gastrochisis in 12.5% (bowel outside the wall of the abdomen at birth)
  - Malrotation in 10% (bowel twists on itself)
  - Aganglionosis in 6% (nerves that control the bowel do not develop)
What is SBS?

• An important fact is how much bowel is left after the surgery ... and what type of bowel it is
  – If no colon is left, a patient has a jejunostomy or ileostomy
  – The shorter this length of jejunum or ileum is, the more likely a patient will need home parenteral nutrition (HPN)
  – Having the valve that controls passage of food between small bowel and colon may also be important
Short Bowel Syndrome

Jejunoileal Anastomosis

Jejunocolic Anastomosis

End Jejunostomy
SBS and HPN

• HPN is needed
  – When the bowel is very short
    • less than 100 cm or 40 inches in adults
    • less than 40 cm in children
  – When much ileum is gone
  – When remaining bowel is diseased
    • Active Crohn’s disease
    • Radiation scaring
    • When bowel just doesn’t work
  – Early after the bowel resection
    • Some patients don’t need HPN for a long time
    • Others do
Risks of HPN

• HPN patients say these factors are most important to them
  – Line infections
  – Survival
  – Quality of life
    • Education about HPN
    • Rapport with HPN team
    • Psychological support
    • Maximal HPN-free days
      – Dreesen, JPEN June 10 2014
Gut Adaptation

• Normal process by which the intestine steps up to do the work (absorbing nutrition from food) of bowel that’s gone
  – Intestine tissue grows in number of cells
  – Takes 1-2 years at least
  – Eating food is important
  – Enteral tube feedings may be used
  – Some drugs may help
Diet to Support Adaptation

- Grazing eating style
- http://www.youtube.com/watch?v=mmOf3u3cuMc
Diet to Support Gut Adaptation

• Complex carbohydrates
  – Pasta, rice, bread, crackers
• Especially white ones
  – Whole grain carbohydrates are harder to digest
• Normally absorbed in the upper small bowel
• Can be absorbed lower in the bowel when you have SBS
• Only if you eat them
Diet to Support Gut Adaptation

• Avoid simple sugars
  – Candy, icing, soda, syrup
• Pull water into the bowel ➔ Diarrhea
Diet to Support Gut Adaptation

• Good quality protein, simply prepared
Diet to Support Gut Adaptation

- Salty foods and fluids
- Salt carries water into cells
  - diarrhea
Diet to Support Gut Adaptation

- Sip salty fluids
- Separate from solid foods
Currently Available New Approaches

• Surgical (STEP)
• Growth factors
  – Growth hormone
  – Glucagon like peptide 2
Serial Transverse Enteroplasty (STEP)

- First reported 2003
- Data from 111 patients
- Infants (age 1-38 months)
- Bowel lengthened

Longer preoperative bowel length predicts full enteral diet

Figure 5. Relationship between preoperative bowel length and the ability to achieve enteral autonomy after the serial transverse enteroplasty procedure (STEP) procedure among the 75 patients in whom preoperative bowel length data were available.
STEP

- Transition to full enteral diet takes time
Somatropin

- Growth hormone (Zorbtive®)
- Approved by FDA for use in adult SBS
- Course is 4 weeks, dose 0.14 mg/kg/d
- Intestinotrophic
- Not advised for patients with history of cancer
Fig. 3. Adverse event profile in patients with short bowel syndrome who were treated with somatropin (SOM) and/or glutamine (GLU). This randomised, double-blind, parallel-group study included patients with short bowel syndrome who were dependent on intravenous parenteral nutrition.[3] Patients received subcutaneous SOM =0.1 mg/kg/day + oral GLU 30 g/day, SOM alone, or placebo (PL) + GLU, for 4 weeks. All patients received a specialised diet. Adverse events occurring in >15% of patients in any treatment arm are reported.
Somatropin vs Absorption

Scolapio, JPEN 1999
- 8 patients, 3 weeks
- 0.14 mg/kg/d growth hormone (GH) + 0.6 g/kg/d oral glutamine powder + high carb low fat diet
- No difference in absorption of fat or fluid
- 3 kg wt gain

Jeppesen, Gut 2000
- 8 patients, 4 weeks
- 0.14 mg/kg/d GH + 30 g oral glutamine powder + usual diet
- No difference in absorption of kcal, carb, fat, nitrogen, wet weight, Na, K, Ca, Mg
- Adverse Events (AE) in all pts on GH, peripheral edema, severe hand pain
Low Dose Somatropin vs Absorption

Ellegard, Ann Surg, 1997
- 10 patients, 8 weeks
- 0.024 mg/kg/d GH + usual diet
- Absorption of fluid, kcal, nitrogen, K, Na, Ca, Mg unchanged
- Mild AEs

Seguy, Gastro 2003
- 12 patients, 3 wk
- 0.05 mg/kg/d GH + no gln + usual diet
- Improved absorption
  - Kcal ↑ 15%
  - Nitrogen ↑ 14%
  - Carb ↑ 10%
- Body weight ↑ 15%
- No AE
Somatropin

- 41 adult HPN patients with SBS
- 4 wk treatment arms
  - 0.1 mg/kg/d GH vs
  - 0.1 mg/kg/d GH+ 30 g/d oral glutamine vs
  - 30 g/d oral glutamine
    • Byrne, Ann Surg 2005; 242:655

- Somatropin permitted significantly more HPN weaning than oral glutamine
- Only somatropin + glutamine + diet maintained reduction for 12 weeks

- AE
  - 94% w peripheral edema,
    44% musculoskeletal complaints
Somatropin

HPN Volume (Liters/week)

Infusions (Days/week)
Weight Change

- No significant change in weight during study
- Weight change after study end attributed to fluid shifts
  - Byrne, Ann Surg 2005; 242:655

![Weight Change Chart]

- **GIn**
- **GH**
- **GIn + GH**

Weeks

Change from Baseline (kg)

-4 -3 -2 -1 0 1 2 3 4

End Follow-up
Growth Factors
Human Growth Hormone in Children

• N=14 children
  – Age 8-10 years
  – HPN dependent 8 years
  – 33 cm small bowel
• 0.14 mg/kg/day growth hormone for 4 months (N=7) vs no treatment (N=7)
• No difference in weaning from HPN
• No effect at 6 months off drug
  – Peretti JPEN 2011; 35:723

• N=8 children
  – Age 3-12 years
  – HPN dependent 4-12 years
  – 5-38 cm small bowel
• Gave 0.12 mg/kg/day for 3 months
• 6 of 8 children weaned off HPN
• At 12 months only 2 of 8 still off HPN
  – Goulet JPEN 2010; 34:513
Summary Somatropin

• In adults, usually 1 month treatment
• In children, 3-4 months
• Most studies show reduced benefit when drug stopped
• Fewer side-effects with lower doses
Glucagon Like Peptide 2 (GLP2)

- Intestinotrophic
- Antisecretory
- ↑ blood flow to the bowel
  - Brenholm, Scand J Gastro 2008

- Studied as Teduglutide, now approved as Gattex®
Teduglutide Clinical Trials

**Inclusion**
- Adults
- ≥ 1 year HPN dependent SBS
- HPN ≥ 3 infusions/week
- Urinary output > 1 L/d
- Urine sodium >20 mmol/d
- Serum Cr, BUN <1.5 × ULN
- LFTs < 2 × ULN

**Exclusion**
- Pregnancy, lactation
- Cancer
- Clinical trial within 30 d
- GLP2 in past 3 m

**Primary Outcome**
- ≥20% reduction in HPN Volume
Teduglutide RCT Flow Chart

O'Keefe, Clin Gastroenterol Hepatol 2013; 11:815-823
HPN Reduction after 12 months, N=52

# Adverse Events

<table>
<thead>
<tr>
<th>AE</th>
<th>0.05 mg/kg/d (N=25)</th>
<th>0.10 mg/kg/d (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>3 (12%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>GI</td>
<td>17 (68%)</td>
<td>17 (63%)</td>
</tr>
<tr>
<td>• Abd distension</td>
<td>4 (16%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>• Abd pain</td>
<td>7 (28%)</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>• Nausea</td>
<td>5 (20%)</td>
<td>11 (41%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>9 (36%)</td>
<td>11 (41%)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (29%)</td>
<td>11 (41%)</td>
</tr>
<tr>
<td>Stoma complication</td>
<td>3 (12%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Catheter sepsis</td>
<td>5 (20%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td><strong>Injection site disorders</strong></td>
<td><strong>13 (52%)</strong></td>
<td><strong>19 (70%)</strong></td>
</tr>
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</table>
Conclusions

- Teduglutide (Gattex®)
  - **Safe** for at least 12 months
    - Adverse events not > placebo
  - **Effective**
    - > 65% patients had > 20% ↓ in HPN volume over 12 months
    - 5/82 patients came off HPN
  - Drug approved by FDA in December 2012
    - Not if history of intestinal cancer
    - Require colonoscopy within 6 months of drug start
    - Insurance coverage
    - **Not approved for children**
Pediatric Teduglutide Study

• Safety study
  – Measure adverse effects after 3 months drug therapy
    • 3 doses of Teduglutide, 1 placebo
  – 36 children age 1-17 years
  – Excluded if
    • STEP in past 3 months
    • Bowel obstruction on xray
    • Major intestinal surgery in past 3 months
    • Untreated intestinal disease
      – www.clinicaltrials.gov
Neonatal Piglets Treated with GLP2 5 days after SBS

A. Body weight gain

B. Intestinal mass

C. Intestinal length

D. Plasma GLP-2

E. Absorption

F. Ex vivo nutrient uptake

Summary

• At present, we use our best available approaches to improve the quality of life and reduce HPN dependence for patients with SBS
  – Diet strategies
  – Gattex in some adults
Thank You
Future Approaches

• Repair the defective gene that results in abnormal bowel in infants ... before birth
• Other therapies to enable gut to grow
  – Peter Nichol, MD, PhD
  – Pediatric Surgeon
  – University of Wisconsin
Future Approaches

• Engineer new intestine
• Animal work so far
  – Tracy Griksheidt, MD
  – Pediatric Surgeon
  – University Southern CA
Future Approaches

• Regenerative medicine to repair or rebuild the intestine
• Stem cell therapy
• Animal models so far
  – Paolo De Coppi, MD, PhD
  – University College London
  – London, United Kingdom