Medical and Surgical Treatments for Short Bowel Syndrome

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Disclosures

• Shire Pharmaceuticals: Consultant
• Zealand Pharma A/S: Consultant
• Vanderbilt Option Care Infusion: Med Dir.

Discussion of off label use of medication will be noted.

Learning Objectives

• Review key concepts to help understand the treatment of SBS
• Discuss the indications, mechanism of action, and side effect of medications used for SBS
• Understand the role of surgery in the management of SBS

Pathway to Enteral Autonomy in Short Bowel Syndrome

Goals of IR Program/Process

• Replete nutrition deficiencies
• Control diarrhea and maintain hydration
• Promote enteral autonomy by optimizing absorptive function
  – Diet and fluid modification
  – Medications for GI disease and symptoms
  – Surgical intervention
• Treat and prevent complications
• Improve quality of life

Short Bowel Syndrome

• Severe intestinal malabsorption that occurs after extensive small bowel resection
• Clinical features include diarrhea, dehydration, electrolyte abnormalities, and malnutrition
Normal Adult GI Anatomy and SBS

SB length: 365-600 cm
Duodenum: ~ 30 cm
Jejunum: ~ 150 to 200 cm
Ileum: ~ 200 to 300 cm
Colon: ~ 150 cm

Short Bowel Syndrome <200 cm of jejunum-ileum (distal to the Ligament of Treitz)

Short Bowel Syndrome
Mechanisms of Malabsorption

Gastric Acid Hypersecretion

- Common after extensive SB resection
- Transient, lasting <4-6 mo
- Pathogenesis: Hypergastrinemia
- Consequences
  - Peptic ulceration
  - Inactivation of pancreatic enzymes
  - Precipitation of bile salts
  - Metabolic alkalosis and hypokalemia

Gastric Antisecretory Medications

- Proton Pump Inhibitor
  - Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
  - Side effects: Abdominal pain, diarrhea, nausea, headache
- Histamine-2 receptor antagonists
  - Cimetidine, famotidine, nizatidine ranitidine
  - Side effects: Diarrhea, constipation, abdominal pain, headache, gynecomasia (cimetidine), hepatitis, low platelets

GI Antisecretory Medications*

- Somatostatin analogue
  - Octreotide (inhibits GH, glucagon, insulin and others)
  - May interfere with intestinal adaptation
  - Side effects: Abdominal pain, diarrhea, nausea, headache, dysrhythmias, hyper/hypoglycemia, hypothyroidism, gallstones
- Alpha-2 adrenergic receptor agonist
  - Clonidine
  - Side effects: Hypotension, dry mouth, abdominal pain, confusion, sleep disorder, rash

*Off label

Rapid Gastrointestinal Transit

- Extensive SB resection; ileum & colon
- Loss of neuroendocrine cells that secrete PYY, GLP-1, GLP-2 and other factors
- Absence of ileocecal valve
- Consequences
  - Rapid gastric emptying
  - Decreased intestinal transit time
  - Increased gastric secretions
Antidiarrheal Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>One dose</th>
<th>Starting dose</th>
<th>Max dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide (Imodium)</td>
<td>2 mg (5 mL)</td>
<td>1 to 2 tablets (5 to 10 mL) PO QID</td>
<td>8 tablets (40 mL)/d</td>
</tr>
<tr>
<td>Diphenoxylate (Lomotil)</td>
<td>2.5 mg (5 mL)</td>
<td>1 to 2 tablets (5 to 10 mL) PO QID</td>
<td>8 tablets (40 mL)/d</td>
</tr>
<tr>
<td>Codeine elixir Tylenol #3</td>
<td>15 mL, 15, 30, 60 mg</td>
<td>15 to 30 mL PO QID</td>
<td>180 mL/d, 360 mg/d</td>
</tr>
<tr>
<td>Opium Tincture</td>
<td>0.3 mL (6 drops)</td>
<td>6 to 20 drops (0.3 to 1 mL) PO QID</td>
<td>120 drops (6 mL)/d</td>
</tr>
</tbody>
</table>

Antidiarrheal meds are most effective if ½ hr to 1 hr before meals

Small Intestinal Bacterial Overgrowth

- Uncommon unless...
  - Blind loop, stricture, internal fistula
  - Increased intestinal transit
  - Decreased gastric acid, pancreatic secretions
  - Absence of ileocecal valve

- Consequences
  - Bacteria consume luminal nutrients
  - Mucosal injury
  - D-lactic acidosis

SIBO Management

- Surgical intervention
- Limit antisecretory and antidiarrheal meds
- Probiotics (over the counter)
- Antibiotics (off label) – 7 day course
  - Amox/Clavulanate 500/125 mg po tid, #21, $63
  - Metronidazole 250 mg po tid, #21, $24
  - Rifaximin 550mg po bid, #14, $$$$$

Quigley, E. Infect Dis Clin N Am 2010;24:943

Other Medications and Supplements

- Bile acid therapy
  - Cholestyramine, colestipol
  - Cholylsarcosine (NA in US)
  - Ox bile (over the counter)
- Pancreatic Enzyme Replacement Therapy

Glucagon-Like Peptide 2 (GLP-2) & Teduglutide (TED)

- Stimulates crypt cell proliferation, inhibits enterocyte apoptosis
- Increases villus height/crypt depth
- Increases nutrient transporter activity
- Increases intestinal blood flow
- Inhibits gastric acid secretion and motility

Heydorn S et al. Scand J Gastroenterol 1999:34:818
**Teduglutide Pivotal Trials**

- Two 24 wk international randomized double-blind placebo controlled trials in 83 and 86 adults
  - Parenteral support ≥12 months
    - 004 trial: 2:2:1 - 0.05mg/kg/d vs. 0.10mg/kg/d vs. PBO
    - STEPS trial: 1:1 - 0.05mg/kg/d vs. PBO
  - Primary end-point = PS reduction was met for both trials 0.05 gm/kg/d

  Jeffes PB, Gut 2011;60:902-914
  Jeffes PB, Gastroenterology 2012;143:1473-81

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**FDA Regulation of Teduglutide**

- REMS: Risk Evaluation and Mitigation Strategy
  - Imposed by FDA to ensure that benefits > risks
  - Risks / precautions:
    - Neoplastic growth
    - Intestinal obstruction
    - Biliary and pancreatic disease
    - Fluid overload
    - Increased absorption of concomitant oral medication
    - Adverse Reactions (>10%: n/v abdominal pain distention, URI symptoms, HA, injection site, fluid overload)

  https://www.gattex.com/hcp/rems.aspx

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**Prescribing and regulatory issues**

- Indication: Adult patient with SBS on PS*
  - Duration of PS is not mentioned
- Prescribers must pass an online course^*
- Dispensed by 5 infusion companies^*
- Maintain SBS registry^ (NCT01990040)
- Case management support from company to assist with drug cost

*FDA REMS
^Prescribing information from package insert

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**Medications for SBS**

<table>
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<tr>
<th>Indication</th>
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<tr>
<td>Gastric acid hypersecretion</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>GI secretion</td>
<td>Histamine-2 Receptor Antagonist</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Alpha-2 adrenergic receptor agonist*</td>
</tr>
<tr>
<td>Small Intestinal Obstruction</td>
<td>Opioid agonist</td>
</tr>
<tr>
<td>Bile acid diarrhea</td>
<td>Bile acid binding resin</td>
</tr>
<tr>
<td>Bile acid deficiency</td>
<td>Bile salt replacement*</td>
</tr>
<tr>
<td>Pancreatic enzyme deficiency</td>
<td>Pancreatic enzyme replacement</td>
</tr>
<tr>
<td>Parenteral support dependent</td>
<td>GLP-2 analogue</td>
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</tbody>
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^Off label  #Over the counter  ^May inhibit adaptation

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**Surgical Management of Short Bowel Syndrome**

- Autologous GI Reconstruction
  - Restore intestinal continuity
  - Strictureplasty

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**Surgical Management of Short Bowel Syndrome**

- Serial Transverse Enteroplasty
- Plication
- Reversed Segment
- Longitude Intestinal Lengthening and Tailoring
Intestinal Transplantation for SBS

Intestinal Failure with

- Failure of HPN (also CMS indications for IT)
  - Impending (bilirubin ≥ 6 mg/dL) or overt liver failure from PN
  - Thrombosis of ≥ 2 central veins
  - Two or more episodes CRBSI / yr of systemic sepsis, one episode of fungemia, septic shock, ARDS
  - Frequent episodes of severe dehydration
- High risk of death
  - Invasive intra-abdominal desmoid tumor
  - Severe SBS: gastro or duodenostomy, < 20 cm SB in adults (10 cm infant)
- High morbidity or poor acceptance of HPN
  - Frequent hospitalization, narcotic dependency, unable to function (pseudointerception, high stoma output)
  - Patient’s unwillingness to accept long-term HPN

References