Latest Updates in Short Bowel Syndrome with Intestinal Failure

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Disclosures

• VectivBio Study Steering Committee
• Takeda Advisory Board
• OWYN, Inc. – Medical Advisory Board
Objectives

- Discuss what Intestinal Failure is
- Define what Short Bowel Syndrome is
- Review normal and abnormal bowel function
- Explain what Intestinal Rehabilitation is
- Discuss newer treatments
Failure – not an unknown term

• F – Failure as in a school grade

• In Medicine,
  - Heart failure
  - Respiratory failure
  - Renal failure
  - Stroke - ?Brain failure?
  - Liver failure
  - Intestinal Failure – not a term readily recognized by Clinicians – not a PubMed term for many years

• What we have is a FAILURE of EDUCATION!!
Definition and Classification of Intestinal Failure

• **Definition**
  - **Intestinal Failure (IF)** - the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that **IV supplementation is required** to maintain health and/or growth.
  
  - While the reduction of gut absorptive function that **doesn't require any IV supplementation** to maintain health and/or growth, can be considered as “**Intestinal Insufficiency**” (II).
Intestinal Failure – May be

- Acquired or Congenital
- Gastrointestinal or Systemic
- Benign or Malignant etiology
- Abrupt onset or from a slowly, progressive chronic illness
- Self-limiting short-term or long-lasting
Classification of Intestinal Failure

- **Functional classification**

  **Criteria - onset, metabolic, and expected outcome**

  - **Type I** - acute, short-term, and often self-limiting condition
  - **Type II** - prolonged acute condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and IV supplementation over periods of weeks or months
  - **Type III** - chronic condition, in metabolically stable patients, requiring IV supplementation over months or years. It may be reversible or irreversible. **Chronic Intestinal Failure = CIF**

Definition and Classification of Intestinal Failure

- **Pathophysiologic classification**
  - Five major conditions which may originate from various gastrointestinal or systemic diseases:
    - Short bowel syndrome
    - Intestinal fistula
    - Intestinal dysmotility
    - Mechanical obstruction
    - Extensive small bowel mucosal disease

Chronic Intestinal Failure
Etiologies

- The most common cause of Chronic Intestinal Failure is surgical resection that results in Short Bowel Syndrome.

- Short Bowel Syndrome
  - Patients with <200 cm of functional small bowel
  - 2 Subgroups
    - Colon in/not in continuity – possible reconnection
    - Total colectomy
  - Important to measure the remaining length of bowel
    - At the time of surgery - best
    - Difficult to measure if the surgery is very remote – Pathology reports
    - Radiologically with an opsiometer

Short Bowel Syndrome Etiologies

- Tumor
- Trauma
- Volvulus
- Bariatric Disasters
- Ischemia/Radiation
- Strangulated hernias
- Surgical complications*
- Inflammatory Bowel Disease
- Thrombosis/embolism of Superior Mesenteric Artery

*Most Common Etiology
Normal Intake and Output

- Oral intake - ~2 L
- Salivary juice - ~1.5L
- Gastric juice - ~2.5L
- Biliary juice - ~0.5L
- Pancreatic juice - ~1.5L
- Intestinal juice - ~1L

About 8-9L in !!

- Urinary losses – ~0.8-1.5L
- GI losses – 100-200gm stool/day
- Insensible losses - ~1L/day
  - Lungs – increased with hyperventilation
  - Skin – evaporation + sweat
- Rapid internal shifts of fluid – 3rd space

Fluid reabsorbed
- Small bowel ~7L (Maximum 12L)
- Colon ~1.4L (Maximum 5L)
Sites of Absorption

Small Intestine
- Carbohydrates
- Fats
- Proteins
- Calcium
- Magnesium
- Trace elements
- Vitamins

Small & Large Intestine
- Water
- Electrolytes
Short Bowel Syndrome
Anatomic Classification Type I, II, III

CIF - SBS - Type I Anatomy
End Jejunostomy

- Micronutrient malabsorption
  - Large sodium and fluid losses
  - Deficient Mg, Vitamin $B_{12}$
- Macronutrient malabsorption
  - If < 100 cm remnant SB past Ligament of Treitz
  - Acid hypersecretion
  - Rapid gastric & intestinal transit
- Poor jejunal adaptation
- Permanent Parenteral Nutrition if < 100 cm SB
- Prognosis to stop PN is poor - fair

Jeejeebhoy KN. Gastroenterology. 2006;137:S60.
CIF - SBS - Type II Anatomy

Jejunocolic Anastomosis

- Potential for adequate calorie & fluid absorption
- < 100 cm TI resection
  - Bile salt diarrhea
  - Possible Vitamin $B_{12}$ malabsorption
- > 100 cm TI resection
  - Fatty acid diarrhea
  - Vitamin $B_{12}$ malabsorption
- Poor jejunal adaptation
- Rapid intestinal transit
- Permanent PN if <65 cm SB
- Prognosis to stop PN is fair

CIF - SBS - Type III Anatomy

Jejuno-Ileal Anastomosis

- Good ileal adaptation
- Preserved absorption of $B_{12}$ and bile salts
- Normal transit
- Usually do well unless there is ileocolonic disease
- Permanent PN if $< 30$ cm SB
- Prognosis to stop PN is good
- Adequate absorption unless $>75\%$ SB resected

- **BUT** - Rarest anatomy type

Jeejeebhoy KN. CMAJ. 2002; 166:1297-1302.
Gut Rehabilitation and Transplant

Cleveland Clinic CGRT Mission Statement:
To enhance absorptive capacity, improve nutritional status, and reduce need for PN through the use of:

- Diet
- Additional fiber
- Oral rehydration solutions
- Specialized nutrients
- Isolated or multivisceral transplant

- Medications
- Enteral nutrition
- Growth factors
- Reconstructive surgery
SBS with Colon: Restrict Fat

High CHO diet significantly increased energy absorption over high fat diet

## Dietary Modification

### WITH COLON
- CHO 50-60% (limit sweets)
- PRO 20%
- FAT 20-30%
- Meals 5-6 daily
- Isotonic fluids
- Fiber as tolerated
- Lactose as tolerated

### NO COLON
- CHO 40-50% (limit sweets)
- PRO 20%
- FAT 30-40%
- Meals 4-6 daily
- Isotonic, high Na fluids
- Fiber as tolerated
- Lactose as tolerated

A Variety of Medications Is Used to Treat Different Aspects of Short Bowel Syndrome (SBS)

- **Gastric Hypersecretion**
  - Histamine type-2 receptor antagonists (H$_2$RAs)
  - Proton pump inhibitors (PPIs)

- **Diarrhea**
  - Antimotility – loperamide, diphenoxylate-atropine, codeine, etc
  - Antisecretory – somatostatin analogs, $\alpha_2$-adrenergic receptor antagonist

- **Steatorrhea**
  - Bile acid sequestrants
  - Pancreatic enzyme replacement therapy (PERT)

- **Bacterial overgrowth**
  - Prebiotics/probiotics
  - Antibiotics

- **Intestinal adaptation**
  - Growth hormone
  - Glucagon-like peptide 2 (GLP-2) analogs
Anti-secretory Agents: Diarrhea

- Somatostatin analogue: Octreotide
  - ↓ GI motility and secretions
- $\alpha_2$-adrenergic receptor antagonist: Clonidine
  - ↓ GI motility and secretions

Nausea/vomiting, obstructive symptoms and hypermotility in select patients

Anti-secretory Agents:
Pancreatic Enzyme Replacement

- Pancreatic enzymes
  - Lipase
    - works with bile to break down fat molecules for absorption
  - Protease
    - breaks down proteins
    - helps keep the intestine free of parasites
  - Amylase
    - breaks down carbohydrates for absorption

Abdominal pain, Abnormal feces, Dizziness, Flatulence and Headache
## Bile Acid Sequestrants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine resin (Questran)</td>
<td>2-4 g dose in liquid just before meals 3x/day</td>
</tr>
<tr>
<td>Colestipol hydrochloride (Colestid):</td>
<td>Granule form: 5g dose 1-4x/d (max 30g/day)</td>
</tr>
<tr>
<td></td>
<td>Tab form: 2g 1-4x/day (max 16g/day)</td>
</tr>
</tbody>
</table>

Small Intestine Bacterial Overgrowth

Ileocecal valve:
- Prevents retrograde flow of bacteria

Causes:
- Obstruction
- Sluggish peristalsis
- Loss of valve
- ↓pH

Treatment:
- Probiotics
- Antibiotics
- Prebiotics

Diagnosis:
- SB aspirate
- Hydrogen breath test

Symptoms
- Gas, bloating, diarrhea, constipation, steatorrhea
- Weight loss, nutrient deficiency
- Fishy body odor, feculent smelling breath, pungent stool odor
# SIBO: Antibiotics

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin (Cipro)</td>
<td>500 mg BID</td>
</tr>
<tr>
<td>Metronidazole (Flagyl)</td>
<td>250 mg TID</td>
</tr>
<tr>
<td>Rifaximin (Xifaxan)</td>
<td>400 mg TID</td>
</tr>
<tr>
<td>Doxycycline (Doxy)</td>
<td>100 mg BID</td>
</tr>
<tr>
<td>Amoxicillin (Amoxi)</td>
<td>500 mg TID</td>
</tr>
<tr>
<td>Tetracycline (Terramycin)</td>
<td>250 mg 4x/d</td>
</tr>
</tbody>
</table>


*7-14 days duration

Possible side effects:
- Diarrhea
- Nausea
- Cramping
- Vomiting
- Abdominal distention
# SIBO - Probiotics

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Form</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Align</td>
<td>Tablet</td>
<td>1-3 tabs/d</td>
</tr>
<tr>
<td>Culturelle</td>
<td>Tablet</td>
<td>1 tab/d</td>
</tr>
<tr>
<td>Primal Defense</td>
<td>Tablet</td>
<td>1 tab/d</td>
</tr>
<tr>
<td>Activia-light</td>
<td>Yogurt</td>
<td>1 per day</td>
</tr>
<tr>
<td>DanActive</td>
<td>Yogurt</td>
<td>1 per day</td>
</tr>
<tr>
<td>VSL #3</td>
<td>Tablet/Powder</td>
<td>1-3 packets/d</td>
</tr>
</tbody>
</table>
Glucagon-like peptide-2

- Enteroendocrine peptide released in response to luminal contents
- GLP-2 Analog (Teduglutide [Gattex])
  - Expensive Therapy
  - Staff intensive
  - Can help villi grow and absorb more
  - Some patients get off IV Nutrition or reduce their need for it
Several Opioid Derivatives Are Options as Antimotility Therapies in Patients With SBS

- Slow transit through the GI tract by reducing intestinal smooth muscle activity, allowing time for greater nutrient absorption
- Use is widespread, with the goals of reducing water/electrolyte losses and minimizing symptoms and consequences of diarrhea
- Use can facilitate ostomy appliances, prevent accidental soiling and skin excoriation, and ease ostomy care
- Loperamide is generally preferred as the 1st-line option due to a lack of addictive or sedative effects
- Other medications – diphenoxylate-atropine, codeine, paregoric, tincture of opium
- **NOTE**: Although antimotility agents are commonly used in patients with SBS, few studies have investigated these medications in the SBS patient population

Teduglutide, a GLP-2 Analog, Has Intestinotrophic Properties

**GLP-2**
- Secreted mainly by cells in distal small bowel and proximal colon
- Mediates increased jejunal absorption through induction of jejunal epithelial proliferation
- Slows gastric emptying and increases intestinal transit time

**Teduglutide**
- GLP-2 analog resistant to enzymatic breakdown
- Intestinotrophic effects include increases in villus height, crypt depth, and mitotic index
- Clinical benefits reverse after treatment discontinuation

Several Factors Affect Intestinal Adaptation and Successful Transition From PN to EN

• Patients at high risk for loss of nutritional autonomy
  - Jejunoileal anastomosis and small bowel <35 cm
  - Jejunocolic anastomosis and small bowel <60 cm
  - End jejunostomy and small bowel <115 cm

• Comorbidities that inhibit adaptation include:
  - Active Crohn’s Disease
  - Radiation enteritis
  - Cancer
  - Pseudoobstruction of remaining bowel

EN = enteral nutrition; PN = parenteral nutrition
Ways to Promote Intestinal Adaptation

• Begin oral or enteral nutrition as soon as possible

• Stimulation of gut with macronutrients

• Feed complex nutrients – polysaccharides and not simple sugars (monosaccharides)
Several GLP-2 Analogs Are Being Investigated in Clinical Trials of Patients With SBS

- Glepaglutide
- Apraglutide
- HM15912
- Also a GLP-1, Vurolenatide is being studied
## Management of Chronic Intestinal Failure

### Patient Centered Care

<table>
<thead>
<tr>
<th>Healthcare Professionals</th>
<th>Medical Care</th>
<th>Psychosocial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenterologist</td>
<td>Dietitian</td>
<td>Diet counseling</td>
</tr>
<tr>
<td>Surgeon</td>
<td>Nurse</td>
<td>Medications</td>
</tr>
<tr>
<td>Interventional Radiologist</td>
<td>PS (PN &amp; IVS)</td>
<td>OLEY Foundation</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>Case Manager</td>
<td>EN</td>
</tr>
<tr>
<td>Stoma therapy</td>
<td>Social Work</td>
<td>Access device management</td>
</tr>
<tr>
<td>Psychologist</td>
<td>Psychiatrist</td>
<td>Autologous Intestinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reconstruction</td>
</tr>
<tr>
<td>Other subspecialists as needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Care Physician</td>
<td></td>
<td>Intestinal Transplant</td>
</tr>
</tbody>
</table>

EN = Enteral Nutrition; IVS = Intravenous Supplementation; PS = Parenteral Support

Matarese LE, et al. JPEN. 2014;38(1 suppl):60S-64S.
Cleveland Clinic

Every life deserves world class care.