Intestinal Failure
*Diet, Drugs and the Knife*

John K. DiBaise, MD
Professor of Medicine
Division of Gastroenterology
Mayo Clinic Arizona
Relevant Disclosures

Commercial Interest
None

Off Label Usage
None
Intestinal Failure

Condition in which inadequate digestion and/or absorption of nutrients/fluids leads to malnutrition and/or dehydration
Intestinal Failure

Etiology

Acute
• Mechanical obstruction
• Ileus
• Intestinal fistulae
• Severe colitis
• Intra-abdominal sepsis

Chronic
• Short Bowel Syndrome
• Pseudo-obstruction (CIPO)
• Radiation enteritis
• Nonresponsive sprue
• Microvillus atrophy
• Autoimmune enteropathy
Learning Objectives

• Review the management of short bowel syndrome
• Describe the diagnosis and treatment of chronic intestinal pseudo-obstruction
• Discuss the current status of intestinal transplantation
Case (1)

- 48 year old male
- Recurrent dehydration, weight loss and electrolyte deficiencies
- Massive intestinal resection 8 months previously
  - SMA thrombosis
  - Negative hypercoagulable state evaluation
- Bowel anatomy unclear
  - ? Half colon and 5 feet of small bowel removed
- 6-12 loose-watery, foul-smelling stools/day
- Poor appetite
- Nausea/dyspepsia
- Constantly thirsty with poor urine output
Case (2)

- **Medications**
  - Pepcid prn, potassium 20 mEq TID, tincture of opium 10 drops TID
  - Biweekly IV fluid w/magnesium
  - No longer on home PN
- **No dietary changes**
- **Drinks a lot of gatorade and water**

- **Examination**
  - BMI 19.1 kg/m² (lost 30% of normal body wt)
  - Orthostatic BP
  - Dry skin/mucus membranes, eczematous rash on hands/feet
- **Stool output** – 2.5 L/day
- **Urine output** – 600 mL/day
- **Labs** – Increased BUN/creatinine, borderline low albumin/calcium, decreased magnesium, zinc, vitamin D, EFA
What Defines Short Bowel Syndrome?

• Wide ranging length
  – 300 to 650 cm

• Tremendous functional reserve
  – Problems when > 75% removed

• < 200 cm small bowel remaining

“It is not how long it is, but what you do with it, my friend...”
Anonymous, about 500 BC
# Causes of SBS

## Infants
- Congenital anomalies
  - Midgut volvulus
  - Gastrochisis
  - Atresia
  - Aganglionosis
- Necrotizing enterocolitis

## Adults
- Postoperative (24%)
- Radiation enteritis/Tumors (24%)
- Mesenteric ischemic events (22%)
- Crohn’s disease (17%)
- Trauma (8%)
- Other (7%)

*Dabney et al. Am J Surg 2004*
Bowel Anatomy Types in SBS

Short Bowel Syndrome

jejunal resection

ileal resection

extensive resection
Complications of SBS

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

- **PN-related**
  - Hepatic
  - Biliary

- **Altered bowel anatomy-related**
  - Fluid/electrolyte disturbances
  - Micronutrient deficiency/excess
  - Oxalate nephropathy
  - Bacterial overgrowth
  - D-lactic acidosis
  - Renal dysfunction
  - Metabolic bone disease
  - Peptic ulcer disease
GI Tract Anatomy/Physiology

Nutrient and Fluid Absorption

Sites of Absorption:
- Iron
- Folate
- Water and electrolytes
- Vitamin B₁₂
- Bile salts
- Short chain fatty acids
- Carbohydrates
- Fats
- Proteins
- Calcium
- Magnesium
- Trace elements
- Vitamins

Normal Fluid Movement:
- Sodium (Na), Chloride (Cl), Water (H₂O)
- Hyperosmolar intake
- Passive permeability
- Jejunum - high
- Ileum - intermediate
- Colon - low
Case (3)

- Initial management
  - Education and counseling
  - High CHO – low fat, low oxalate diet
  - Restrict hyperosmolar fluids
  - Oral rehydration solution
  - PPI bid
  - Imodium 2 tablets ac/hs
  - MVI, zinc, oral mag oxide, calcium w/vit D, essential fatty acid supplement
  - Changed B12 injection to monthly
Treatment Options in SBS

- Diet
- Fluids
- Medications
  - Antimotility
  - Antisecretory
  - Bile acids
  - Antibiotics
  - Trophic factors
- Nutrition support
  - Parenteral
  - Enteral
  - Combination
- Surgery
  - Autologous GI reconstruction
  - Transplantation
### Dietary Modification

<table>
<thead>
<tr>
<th>COLON PRESENT</th>
<th>COLON ABSENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Encourage hyperphagia</td>
<td>• Encourage hyperphagia</td>
</tr>
<tr>
<td>• CHO 50-60%</td>
<td>• CHO 40-50%</td>
</tr>
<tr>
<td>• PRO 20%</td>
<td>• PRO 20%</td>
</tr>
<tr>
<td>• FAT 20-30%</td>
<td>• FAT 30-40%</td>
</tr>
<tr>
<td>• Meals 5-6 daily</td>
<td>• Meals 4-6 daily</td>
</tr>
<tr>
<td>• Avoid oxalates</td>
<td>• Oxalates: no restriction</td>
</tr>
<tr>
<td>• Isotonic/hypoosmolar fluids</td>
<td>• Isotonic, high Na fluids</td>
</tr>
<tr>
<td>• Soluble fiber 5-10 g/day</td>
<td>• Soluble fiber 5-10 g/day</td>
</tr>
<tr>
<td>• Lactose as tolerated</td>
<td>• Lactose as tolerated</td>
</tr>
</tbody>
</table>

*Byrne et al. NCP 15:306, 2000*
*Norgaard et al. Lancet 1994*
*Jeppesen et al. Gut 1998*
Fluids in SBS – Importance of ORS

• End-jejunoscopy require glucose-electrolyte solution (ORS)
  – 90 mEq/L sodium
• Fluid composition less important to those with a colon
• All should avoid hyperosmolar fluids
Antisecretory Agents in SBS

• Massive enterectomy associated with transient (6-12 mo) hypergastrinemia and hypersecretion

• H₂RA or PPI may be beneficial

*Cortot et al. N Engl J Med 1979*
Somatostatin Use in SBS

• Decreases a variety of GI secretions and slows gastric and jejunal transit
• No clear effect on improving nutrient/fluid absorption
  – Short-lasting, expensive, requires injection
  – Increases risk of gallstones
  – May inhibit bowel adaptation
• May be useful in high stool output conditions

Nehra et al. Am J Gastroenterol 2001
O’Keefe et al. Gastroenterology 1994
Antimotility Agents in SBS

• Decrease motility and reduce secretion
  – Loperamide: minimal side effects; OTC
    • 2 to 4 mg ac/hs
  – Diphenoxylate with atropine
    • 2.5 to 5 mg ac/hs
  – Codeine phosphate
    • 30 to 60 mg ac/hs
  – Opium tincture
    • 5 to 20 drops ac/hs
    • (5 drops=0.25 mL=2.5 mg morphine)

Antimicrobial Use in SBS

**Bacterial Overgrowth**

- Multifactorial pathophysiology
- Variety of potential clinical consequences
  - May interfere with PN weaning and predispose to bacterial translocation
  - May be beneficial in CHO salvage
- Unique diagnostic challenge
  - Small bowel aspirate best test (?)
- Antibiotic therapy first line
  - Improved gas-related symptoms, reduction in stool output and/or weight gain

*DiBaise et al. CGH 2006*
Bile Salt and Pancreatic Enzyme Replacement in SBS

- Bile salt depleted when > 100 cm distal ileum resected
- **Ox bile supplements** and cholylsarcosine
  - Open-label case reports
- Use of bile acid binders (e.g., cholestyramine) to be avoided
  - Worsen fat malabsorption
  - Only use when < 100 cm terminal ileum removed
- No evidence of reduced pancreatic secretion in SBS
- Potential for mismatch of food and enzyme mixing
Case (4)

• Further course (3 months later)
  – BMI 22 kg/m2
  – Good appetite, no longer thirsty
  – Stool volume - < 1 L/d
  – Urine output - > 1 L/day
  – Labs normal including magnesium
Problem with Current Approaches

- PN still frequently necessary
  - Does not enhance bowel function
  - Costly (> $100K/yr)
  - Reduced quality of life
  - 1–2 hospitalizations annually/patient

Howard et al. Gastroenterology 1995
Tokars et al. Ann Int Med 1999
Risk Factors for Permanent Intestinal Failure

• Remnant bowel length
  – ≤ 100 cm end-jejunostomy
  – ≤ 65 cm jejunocolic anastomosis
  – ≤ 30 cm jejunointestinal anastomosis

• Residual disease in remnant bowel

• Absence of colon

• Time on PN
  – ≥ 2 yrs adults; ≥ 4 yrs children

• Degree to which adaptation has occurred

• Age

• Nutritional status

• Fasting plasma citrulline level < 20 μmol/L

• Wet weight absorption < 1.41 kg/d

• Energy absorption < 84%/d

Messing et al. Gastroenterology 1999
Jeppesen and Mortensen 2003
Is there a Role for Enteral Nutrition in SBS?

- Facilitate weaning from PN when oral intake insufficient
  - Gastric, continuous administration
  - Tube feeding improves intestinal absorption in SBS

- 61 adults with SBS (50 cm SB) who received EN + PN (+ GH, glutamine, optimized diet) – 50 ± 24 mo f/u
  - EN comprised about 53 ± 13% of total daily calories
  - 52/61 (85%) successfully weaned from PN
  - 5 remained on both PN + EN

DiBaise JK, et al. JCG 2006
Trophic Factors

• Facilitate intestinal adaptation

• **Intestinal adaptation**
  – Remaining bowel attempts to increase fluid/nutrient absorption to that occurring before resection
  – Variety of stimulators of adaptation
RCT of r-hGH, Glutamine and Specialized Oral Diet

- Patients receiving r-hGH + GLN (n=16)
- Patients receiving r-hGH w/o GLN (n=15)
- Controls received GLN + diet (n=9)
- 4 wks treatment w/12 wks follow-up

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

83 PN-dependent SBS patients

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

24 weeks

Placebo (n=16)

Teduglutide 0.05 mg/kg/d (N=35)

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

Results
6.3% PN ↓
31.3% AEs

*45.7% PN ↓
*LBM 632g ↑
*Citr +10.9 ↑
37.1% AEs

25% PN ↓
*LBM 1527g ↑
*Citr +15.8 ↑
34.4% AEs

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

- Goal is to preserve as much bowel as possible
  - Restore continuity
  - Relieve obstruction
  - Repair fistulae
  - Recruit bypassed/unused bowel
Autologous GI Reconstruction in SBS

• Choice of surgical therapy influenced by
  – Existing bowel length, function and caliber
  – Existing intestinal complications

• Optimize function
  – Increase length (Bianchi, STEP)
  – Taper dilated segment

• Slow transit
  – Reversed intestinal segment

Thompson JS. Surgery 2004
Sudan et al. JOGS 2005
Case (1)

- 56 year old woman
- GI problems began about 3 yrs ago
  - Episodic initially
  - Abdominal distension, pain, nausea, vomiting, 100 # weight loss
- 2 explor. laps unrevealing
- SBS – diffusely dilated SB
- Did not tolerate TF via G-tube
  - Using tube for venting
- On HPN

- PMH – hypothyroid, recurrent UTI, osteoporosis, depression, recent CDI
- PE – chronically ill appearing and thin, tinkling bowel sounds with G-tube
- Labs
  - albumin 2.3, mild microcytic anemia and thrombocytopenia, low vitamin D and selenium, normal electrolytes and liver tests, normal CRP and paraneoplastic Ab panel
  - positive ANA and ENA screen with positive RNP and SSA; CPK, SCL70 Ab and anti-centromere Ab negative
Intestinal Pseudo-Obstruction

• Recurrent symptoms suggestive of intestinal obstruction without evidence of mechanical obstruction
Intestinal Pseudo-Obstruction

• Acute
  – Ileus
    • post-op
    • sepsis
    • drug/toxin-induced

• Chronic
  – Primary
    • neuropathy/myopathy
    • inherited/sporadic
  – Secondary
    • muscle disorders
    • metabolic disorders
    • neurologic disorders
    • Iatrogenic
  – Idiopathic
Causes of Secondary CIPO

- Small bowel diverticulosis
- Metabolic disorder
- Mitochondrial disorders
- Medications
- Paraneoplastic
- Infections
- Radiation enteritis
- Celiac sprue
- Muscular Disorders
- Neuropathic disorders
- CNS lesion
Clinical Presentation of CIPO

- Early satiety/postprandial bloating/distension (85%)
- Nausea/Vomiting (62%)
- Abdominal pain (96%)
- Constipation (45%)
- Diarrhea (40%)
- Weight loss (78%)
- Dysphagia (5%)
- Fecal incontinence

- Systemic complaints
- Insidious onset
- May be asymptomatic between episodes
- May have constant symptoms
- Spectrum of severity
- Narcotic dependence

Lindberg G et al. Scand J Gastro 2009
Complications of CIPO

- Intestinal Failure
- Nutritional deficiencies
- Bacterial overgrowth
- Pneumatosis intestinalis
- Perforation
- Mechanical obstruction
- Extraintestinal (GU, autonomic dysfunction)
- Depression, anxiety, increased suicide risk
Pathophysiology of CIPO

- Neuropathy
  - Inflammatory
  - Degenerative
- Myopathy
- Mesenchymopathy
  (Interstitial cells of Cajal)
Diagnosis of CIPO

• Exclude mechanical obstruction

• Investigate motility
  – Transit (scintigraphy)
  – Manometry (neuropathy vs. myopathy vs. normal)

• Evaluate for secondary causes
  – Neuropathy: autonomic tests, full-thickness biopsy
  – Myopathy: CPK, SCL70, ANNA, Fat pad biopsy

• Role of intestinal neuropathology unclear
Natural History of CIPO

• Diagnosis often delayed (median, 8 yrs)
• Majority (52/59) underwent surgeries (mean, 3/patient)
• Long-term outcome generally poor (59 pts; median, 4.6 yr follow-up)
  – Majority experienced disabling complications
  – 4 died of disease-related complications
  – One-third required home PN
  – Two-thirds with nutritional limitations
  – 4 underwent intestinal transplantation

Stanghellini et al. Clin Gastroenterol Hepatol 2005
Natural History of CIPO in Patients on HPN

- 51 adults (18 male)
- Median age at symptom onset – 20 yrs (0-74)
- Mean follow up – 8.3 yrs (0-29)
- Mean # surgeries – 3 (SBS in 37%)
- Decreased mortality
  - Able to resume PO intake and symptom onset < 20 yrs

Amiot A et al. Am J Gastroenterol 2009
Natural History of CIPO vs. ED

- 55 pts with CIPO (41 F; 42 yrs) and 70 pts with ED (63 F; 39 yrs)
- 12 year follow-up (5.2 – 20.1 yrs)
- Mortality – 35% CIPO vs. 13% ED
  - Sepsis d/t PN most common
  - Suicide in 3 ED and 2 CIPO

Lindberg G et al. Scand J Gastroenterol 2009
Summary of CIPO Treatments

- Dietary modifications
  - Pharmacological
    - Prokinetics
    - Antiemetics
    - Antisecretory agents
    - Immunosuppressants
    - Treat constipation
    - Treat SIBO
    - Combination

- Surgical
  - Venting gastrostomy
  - Feeding jejunostomy
  - Segmental resection
  - Electrical stimulation
  - Transplantation

- Nutrition support
  - Parenteral
  - Enteral
Dietary Modification

• Optimize nutrition and hydration
• Recommendations:
  – Small, frequent meals
  – More liquid calories
  – Restrict fat and residue
  – Be cognizant of vitamin deficiencies
  – Ensure proper hydration
  – Consider dietary counseling with R.D.
Prokinetic Agents

- Cholinergic agonists
  - Bethanechol
- Dopamine antagonists
  - Metoclopramide
  - Domperidone
- Macrolides
  - Erythromycin
- Others
  - Octreotide
  - Leuprolide
  - Misoprostol
  - Pyridostigmine
Response to Prokinetic Agents in CIPO

Surgical Options

• **Jejunal feeding tube**
  – Failed diet and drugs
  – Trial of nasojejunal feeding useful

• **Venting gastrostomy, jejunostomy, cecostomy tubes**
  – Severely symptomatic
  – Failed diet and drugs
  – Trial of NG suction useful
Electrical Stimulation
Case (2)

• Felt to have visceral myopathy due to a CTD - ? MCTD vs. systemic sclerosis sine scleroderma
  – Rheumatology did not recommend any specific immunomodulator therapy
• Additional treatments
  – GI dysmotility diet as tolerated
  – Venting G-tube as needed
  – Low dose Octreotide at bedtime
  – PO erythromycin ac/hs
  – PPI daily
  – Home parenteral nutrition support
Intestinal Transplantation
History of Intestinal Transplantation

• Technical feasibility established over a century ago
• Introduction of cyclosporine (1978)
• First transplant with medium-term success (1988)
• Introduction of tacrolimus (1990s)
• Preoperative induction therapy with monoclonal lymphocyte depleting antibodies (2000s)
Intestinal Transplantation

• **Indications**
  – Irreversible intestinal failure with need for life-long PN and complication of PN

• **Options**
  – Isolated intestinal transplant
  – Combined with liver transplant
  – Multivisceral transplant
Intestinal Transplantation Registry 1985-2003

- 61 programs; 19 countries; 989 grafts in 923 pts
  - Only 28 programs with transplants in last 2 yrs
  - 10 centers performed 83% of all transplants
  - 76% performed in U.S.
- 61% ≤ 18 yrs of age
- More isolated bowel transplants in adults
- More combined bowel/liver transplants in peds

Grant et al. Ann Surg 2005
**Intestinal Transplant Registry**

**Indications**

- **Pediatric**
  - SBS
    - Gastrochisis (21%)
    - Volvulus (17%)
    - NEC (12%)
    - Other (5%)
  - CIPO (9%)
  - Hirschsprung’s (7%)
  - Malabsorptive conditions (9%)

- **Adult**
  - SBS
    - Mesenteric ischemia (23%)
    - Crohn’s (14%)
    - Trauma (10%)
    - Volvulus (7%)
    - Other (9%)
  - CIPO (8%)
  - Desmoid (9%)

*Grant et al. Ann Surg 2005*
Patient and Graft Survival Among Intestinal Transplantation Recipients

- 1-yr graft/patient survival: 58%/65%
  - Better since 1998:
    - Graft: up to 65%
    - Patient: up to 77%
  - Better in home vs. hospitalized patients:
    - Graft: 70% vs. 51%
    - Patient: 78% vs. 72%

Grant et al. Ann Surg 2005
Intestinal Transplantation Registry


• 406 pts alive for > 6 mo at time of data collection
  – 81% off TPN
  – 6.4% require partial TPN
  – 3.9% require IVF
  – 7.9% on full TPN (graft removal)

Grant et al. Ann Surg 2005
Mortality Related to Intestinal Transplantation

• Causes of death: 434/919 died (48%)
  – Sepsis (46%)
  – Graft rejection (11.2%)
  – PTLPD (6.2%)
  – Respiratory (6.6%)
  – Technical (6.2%)
  – MOFS (2.5%)
  – Graft thrombosis (3.2%)
  – Other (17.3%)

Grant et al. Ann Surg 2005
Indications for Referral to Intestinal Transplant Center

• Impaired venous access
  – ≤ 2 neck sites with loss of at least 1 groin site
  – ≤ 1 neck site with both groin sites available

• Line sepsis
  – Recurrent severe sepsis with ≥ 2 line changes in a year
  – Recurrent fungal sepsis

• PN-related liver disease
  – Impending or overt liver failure

• Requirement for extensive enterectomy
Take-Home Points

• Management requires multidisciplinary approach

• Specific dietary intervention combined with careful medical management and occasionally surgery represents standard of care

• Intestinal transplantation appears promising