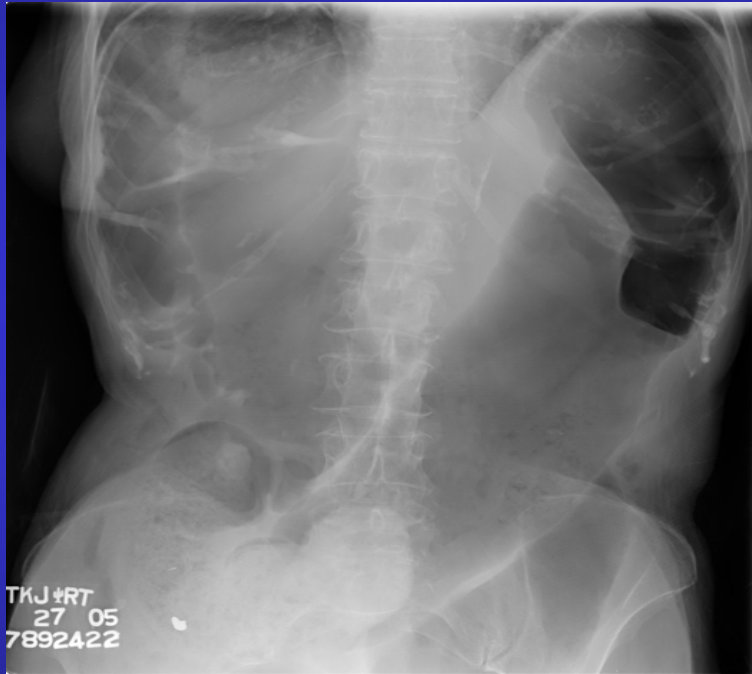




Intestinal Failure

Diet, Drugs and the Knife



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

Relevant Disclosures

Commercial Interest

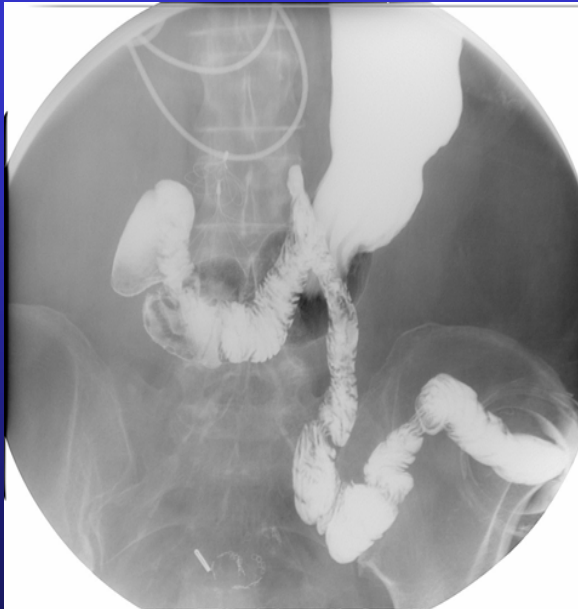
None

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
 - Gastroschisis
 - Atresia
 - Aganglionosis
- Necrotizing enterocolitis

Adults

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

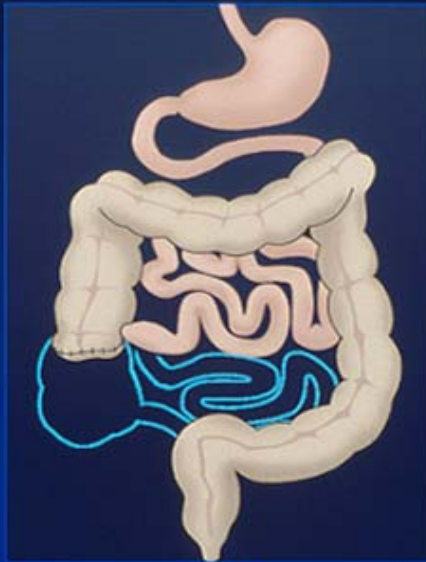
Dabney et al. Am J Surg 2004

Bowel Anatomy Types in SBS

Short Bowel Syndrome



**jejunal
resection**



**ileal
resection**



**extensive
resection**



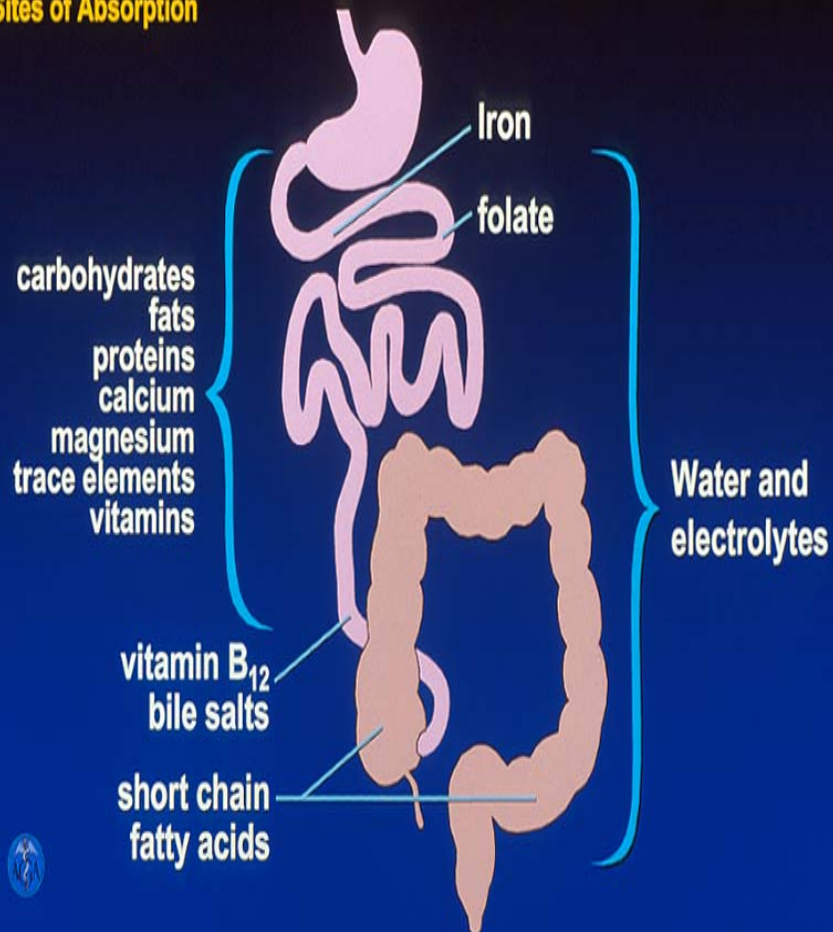
Complications of SBS

- 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

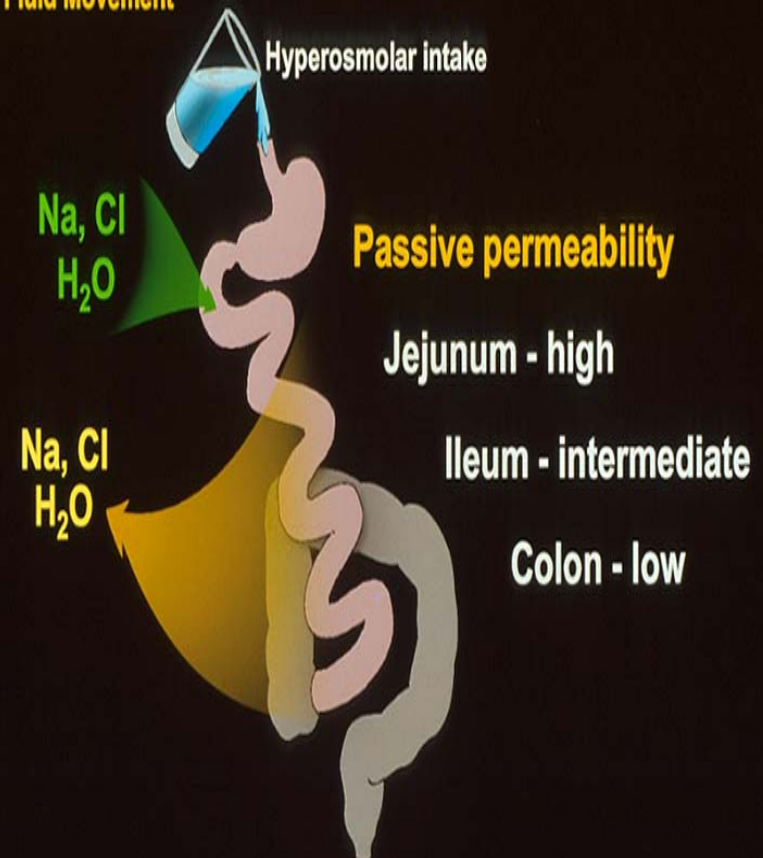
GI Tract Anatomy/Physiology

Nutrient and Fluid Absorption

Sites of Absorption



Normal Fluid Movement



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

COLON PRESENT

- Encourage hyperphagia
- CHO 50-60%
- PRO 20%
- FAT 20-30%
- Meals 5-6 daily
- Avoid oxalates
- Isotonic/hypoosmolar fluids
- Soluble fiber 5-10 g/day
- Lactose as tolerated

COLON ABSENT

- Encourage hyperphagia
- CHO 40-50%
- PRO 20%
- FAT 30-40%
- Meals 4-6 daily
- Oxalates: no restriction
- Isotonic, high Na fluids
- Soluble fiber 5-10 g/day
- Lactose as tolerated

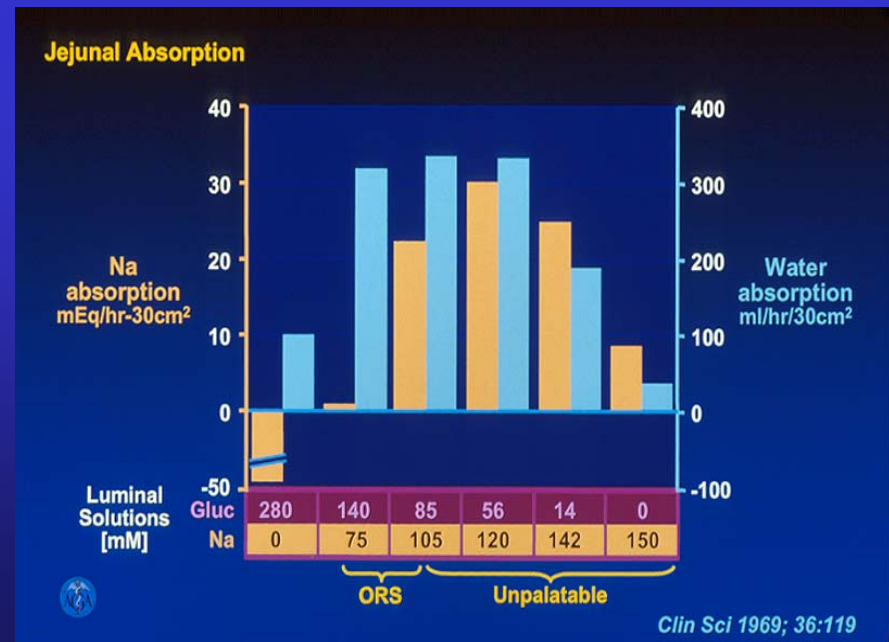
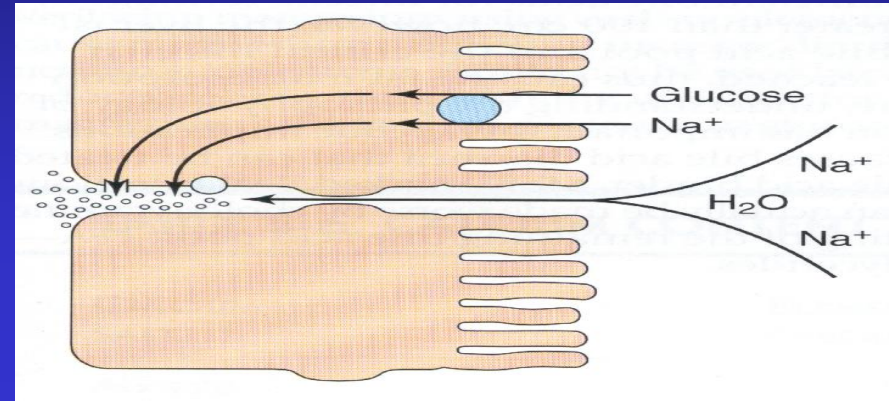
Byrne et al. NCP 15:306, 2000

Norgaard et al. Lancet 1994

Jeppesen et al. Gut 1998

Fluids in SBS – Importance of ORS

- End-jejunostomy 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)

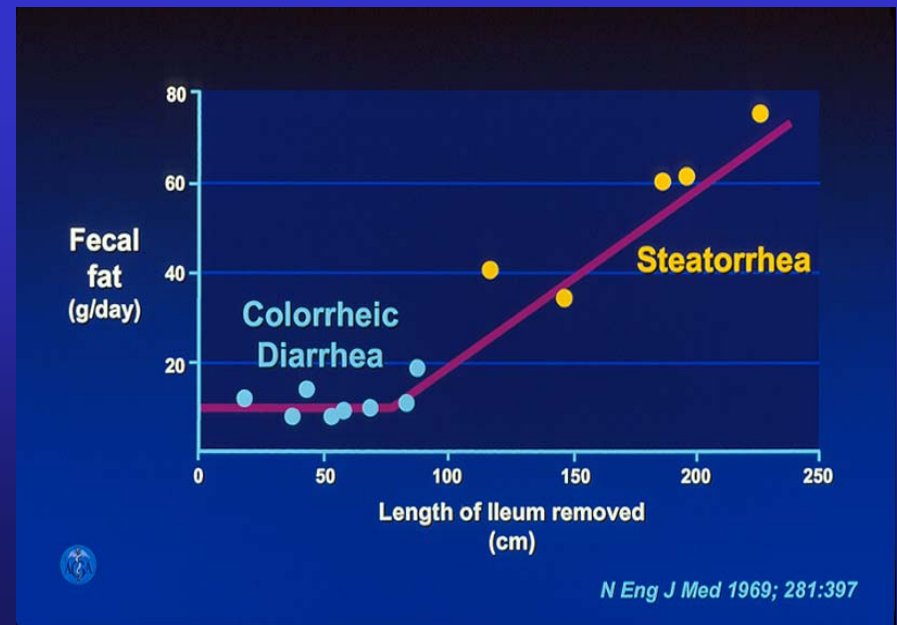
Antimicrobial Use in SBS

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

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

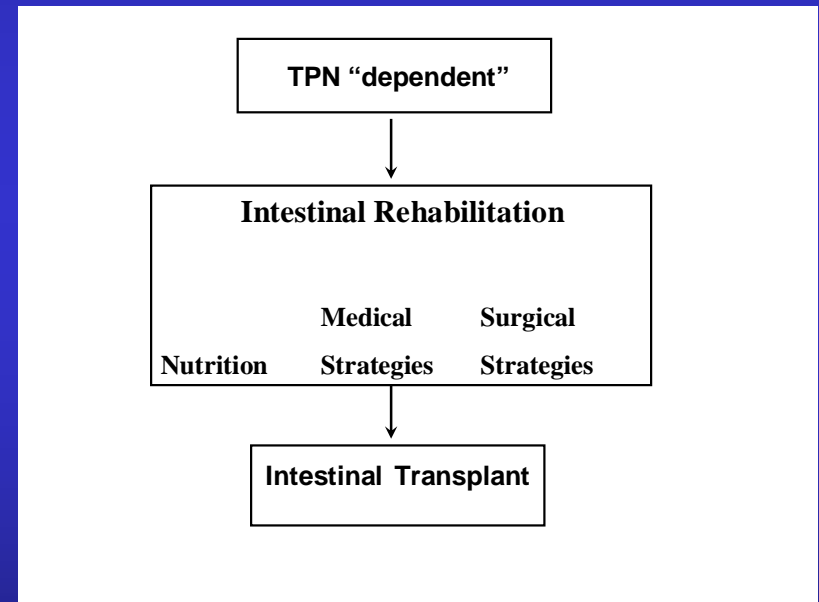


Case (4)

- 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
Cavicchi et al. Ann Int Med 2000

Risk Factors for Permanent Intestinal Failure

- Remnant bowel length
 - ≤ 100 cm end-jejunostomy
 - ≤ 65 cm jejunocolic anastomosis
 - ≤ 30 cm jejunoileocolic 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 $< 20 \mu\text{mol/L}$
- Wet weight absorption $< 1.41 \text{ kg/d}$
- Energy absorption $< 84\%/d$

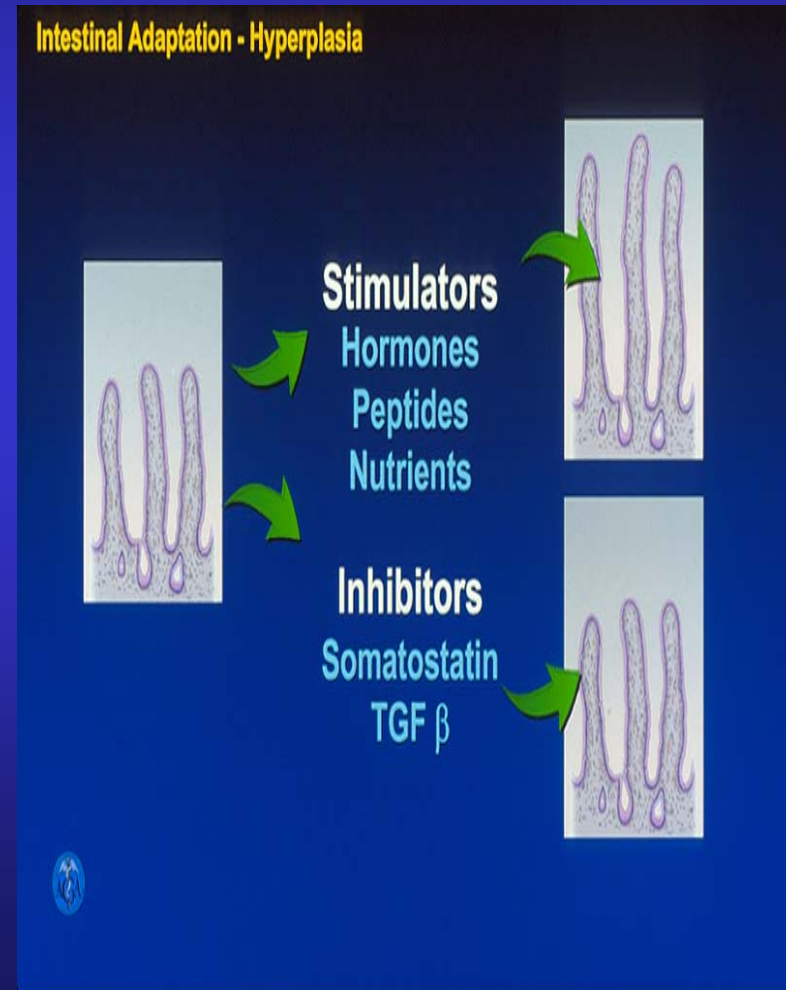
Messing et al. Gastroenterology 1999
Jeppesen and Mortensen 2003

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
 - Joly F, et al. Gastro 2009*
 - DiBaise JK, et al. JCG 2006*
- 61 adults with SBS (50 cm SB) who received EN + PN (+ GH, glutamine, optimized diet) – 50 ± 24 mo f/u
 - EN comprised about $53 \pm 13\%$ of total daily calories
 - 52/61 (85%) successfully weaned from PN
 - 5 remained on both PN + EN
 - Gong JF, et al. Asia Pac J Clin Nutr 2009*

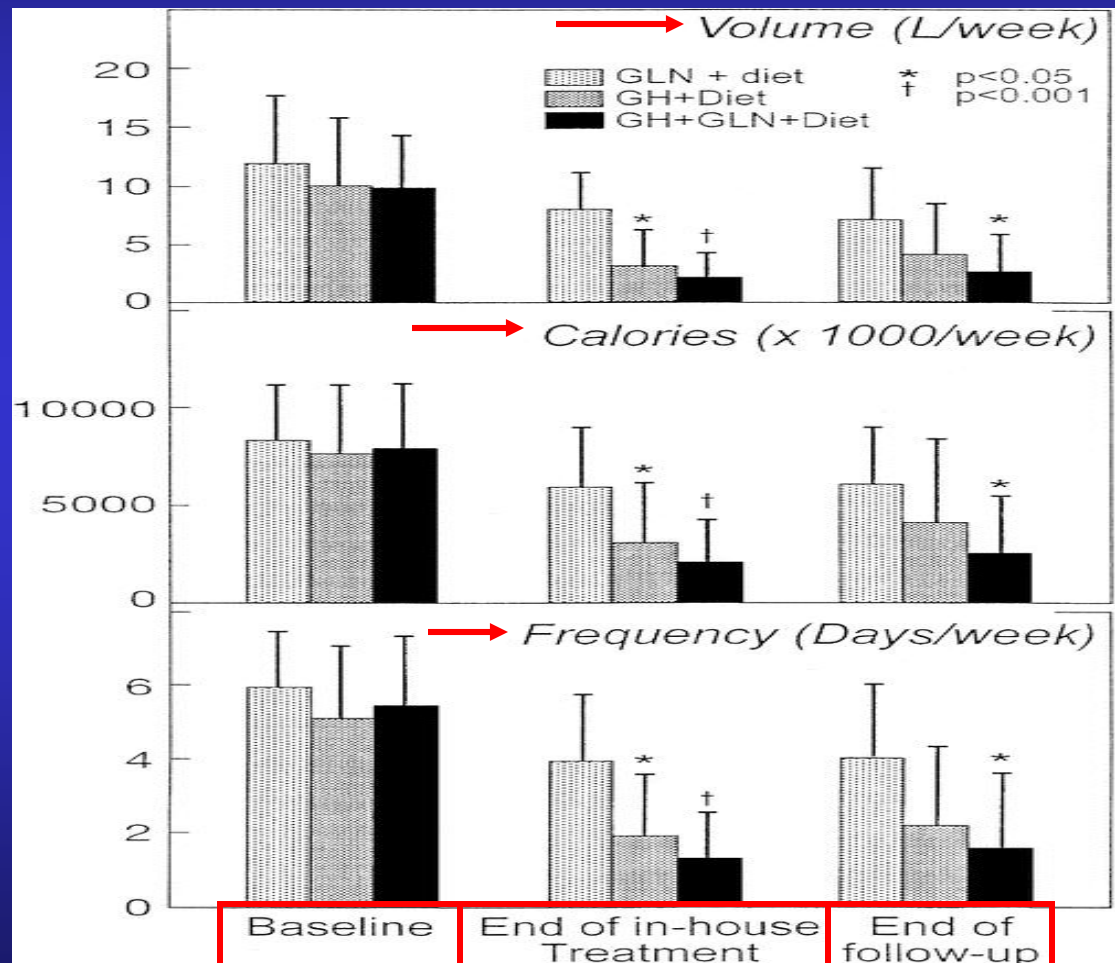
Trophic Factors

- Facilitate intestinal adaptation
- Intestinal adaptation
 - Remaining bowel attempts to increase fluid/nutrient absorption to that occurring before resection
 - Variety of stimulators of adaptation



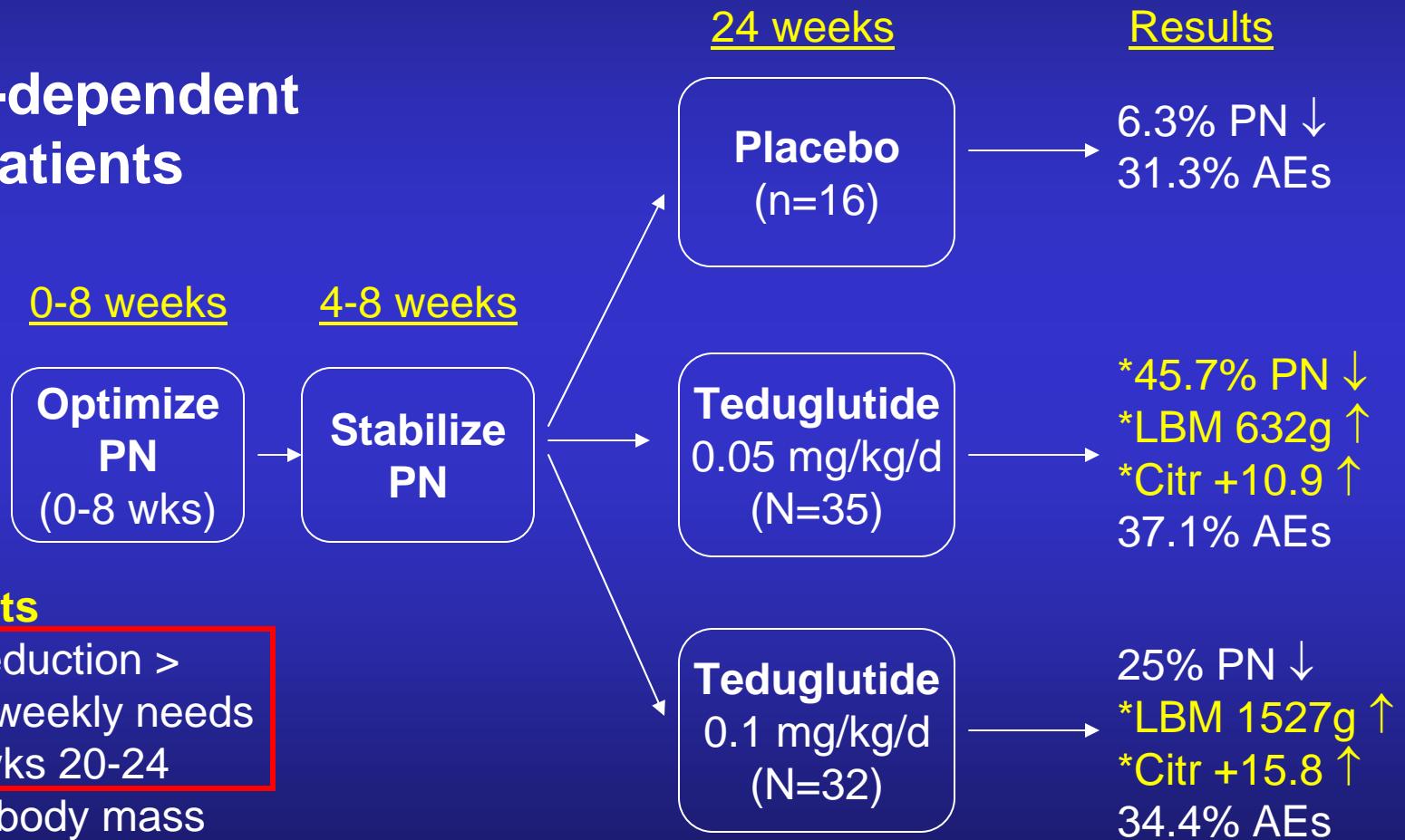
RCT of r-hGH, Glutamine and Specialized Oral Diet

- 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

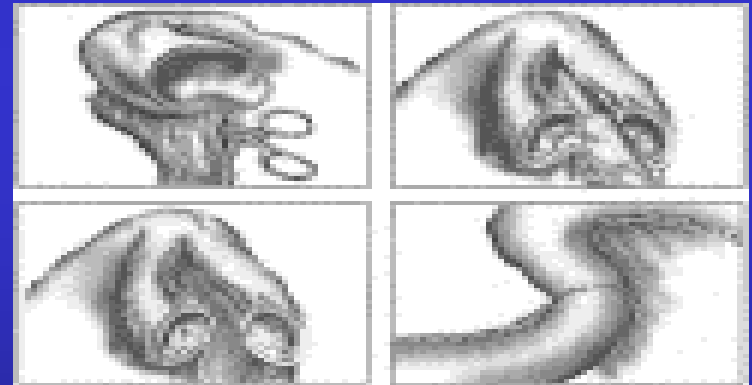
Surgery in SBS

- Goal is to preserve as much bowel as possible
 - Restore continuity
 - Relieve obstruction
 - Repair fistulae
 - Recruit bypassed/unused bowel



Autologous GI Reconstruction in SBS

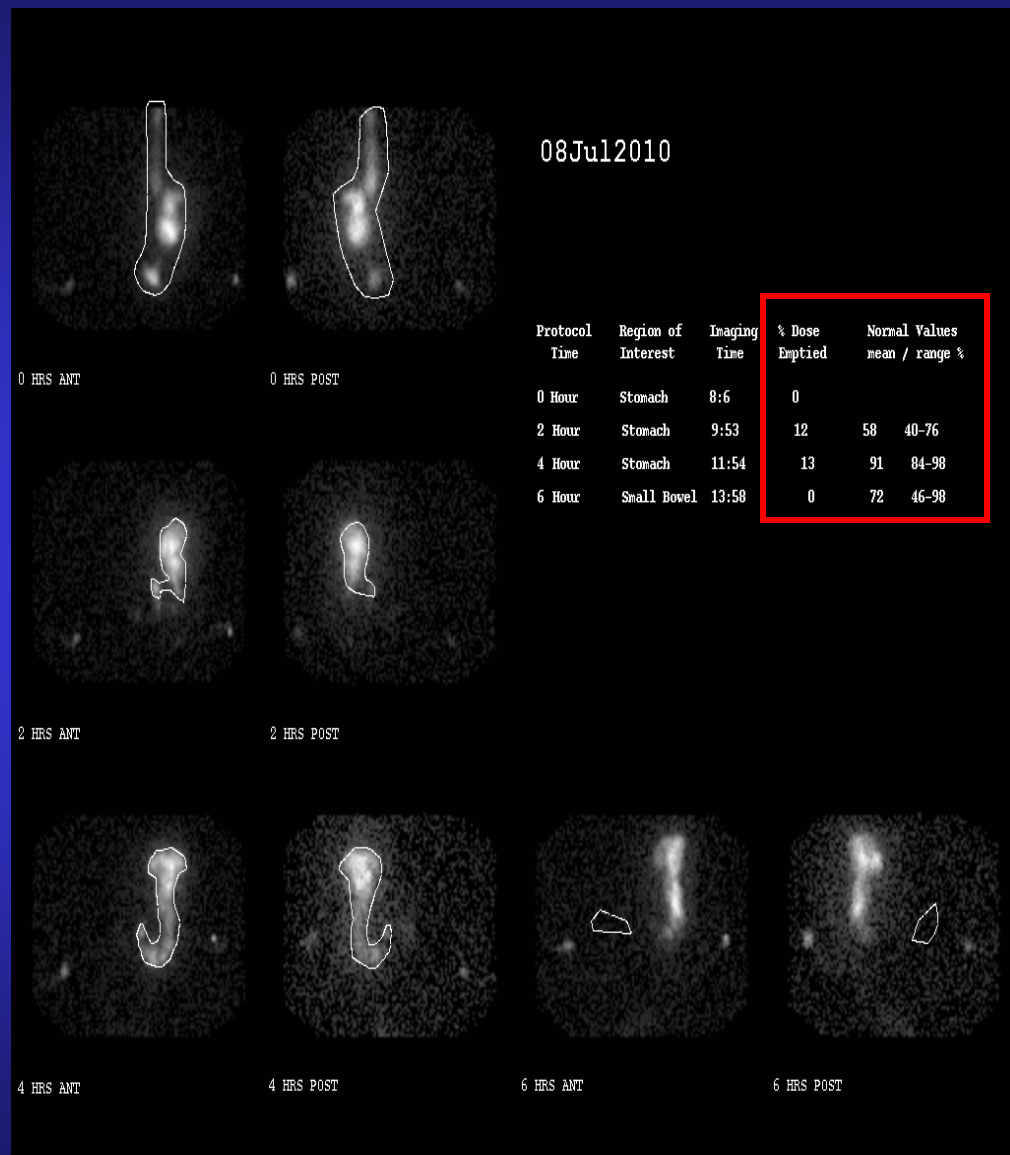
- Choice of surgical therapy influenced by
 - Existing bowel length, function and caliber
 - Existing intestinal complications
- **Optimize function**
 - Increase length (Bianchi, STEP)
 - Taper dilated segment
- **Slow transit**
 - Reversed intestinal segment



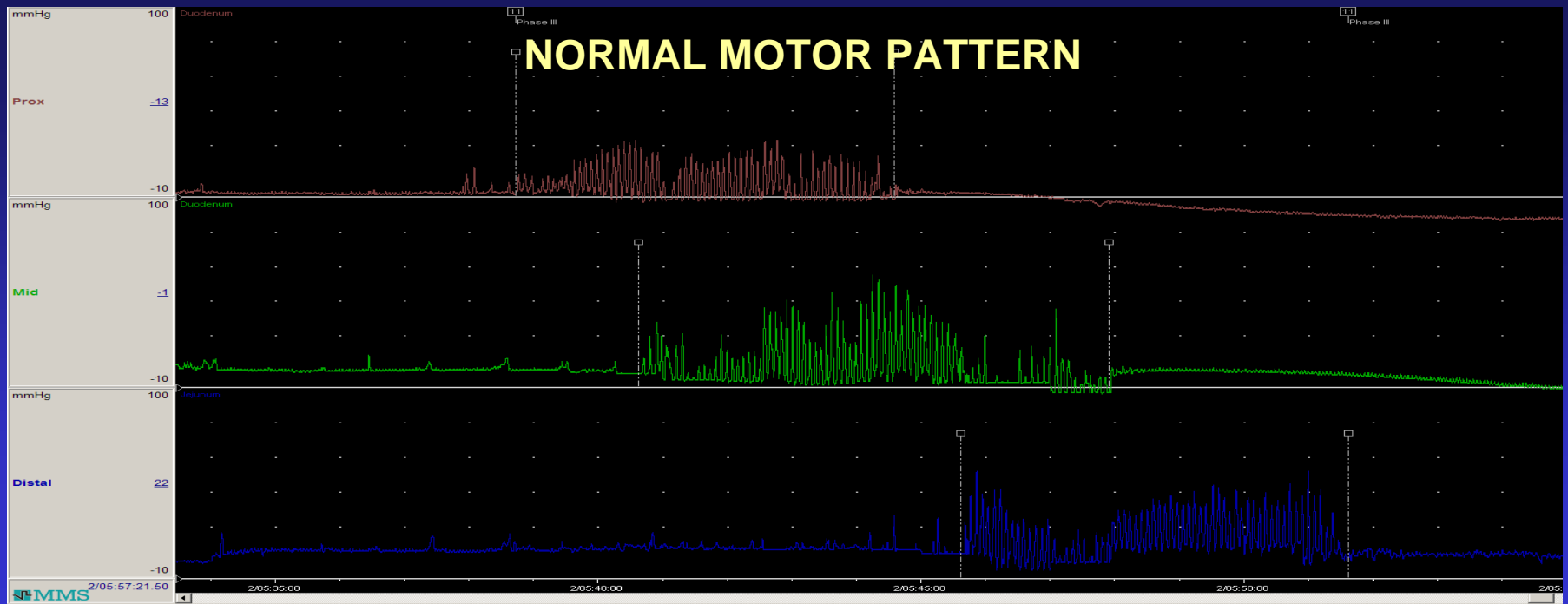
Thompson JS. Surgery 2004
Sudan et al. JOGS 2005

Case (1)

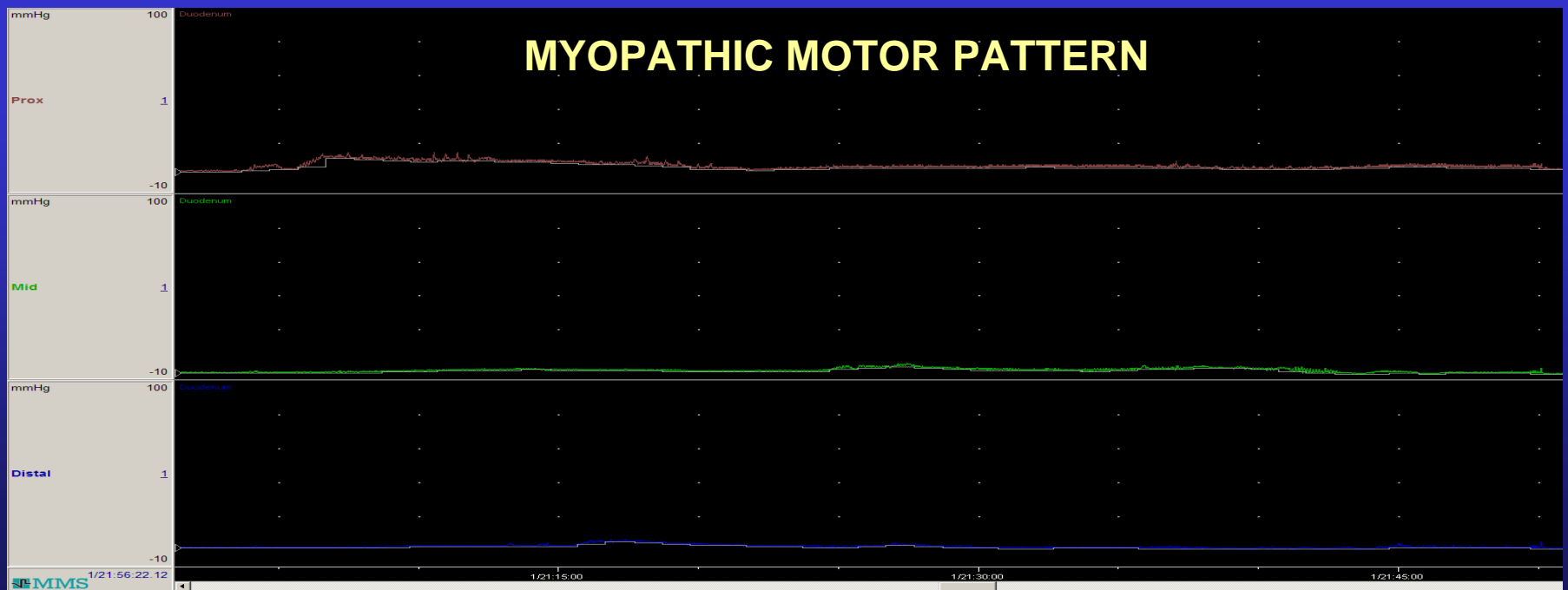
- 56 year old woman
- GI problems began about 3 yrs ago
 - Episodic initially
 - Abdominal distension, pain, nausea, vomiting, 100 # weight loss
- 2 explor. laps unrevealing
- SBS – diffusely dilated SB
- Did not tolerate TF via G-tube
 - Using tube for venting
- On HPN
- PMH – hypothyroid, recurrent 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 paraneopl Ab panel
 - **positive ANA and ENA screen with positive RNP and SSA; CPK, SCL70 Ab and anti-centromere Ab negative**



NORMAL MOTOR PATTERN

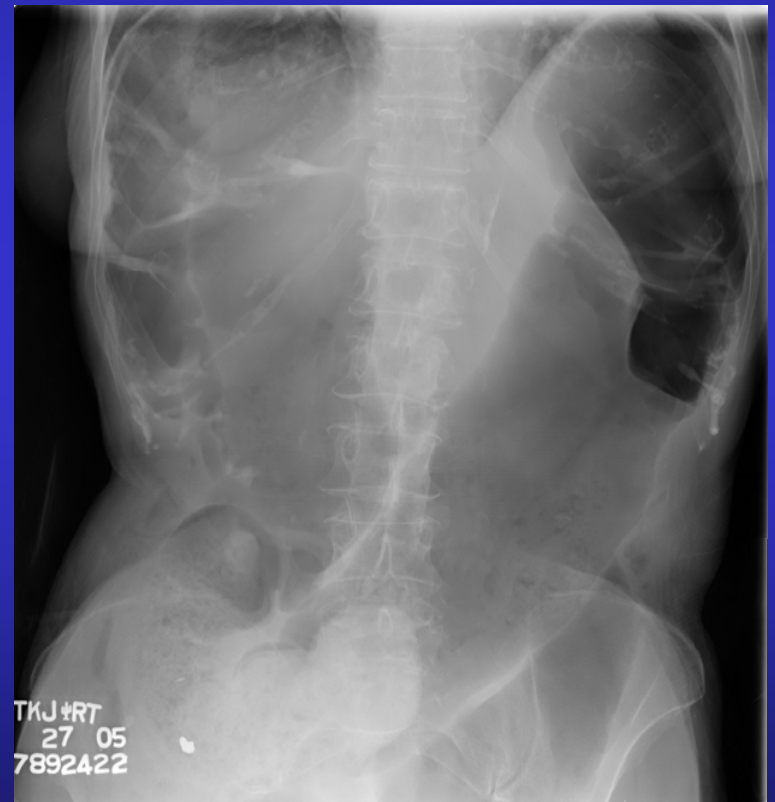


MYOPATHIC MOTOR PATTERN



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

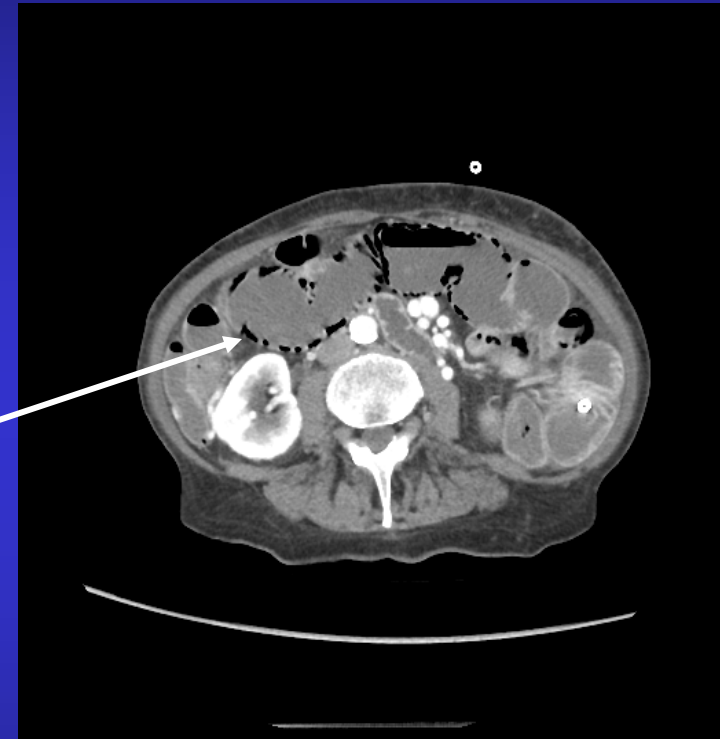
- Small bowel diverticulosis
- Metabolic disorder
- Mitochondrial disorders
- Medications
- Paraneoplastic
- Infections
- Radiation enteritis
- Celiac sprue
- Muscular Disorders
- Neuropathic disorders
- CNS lesion

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

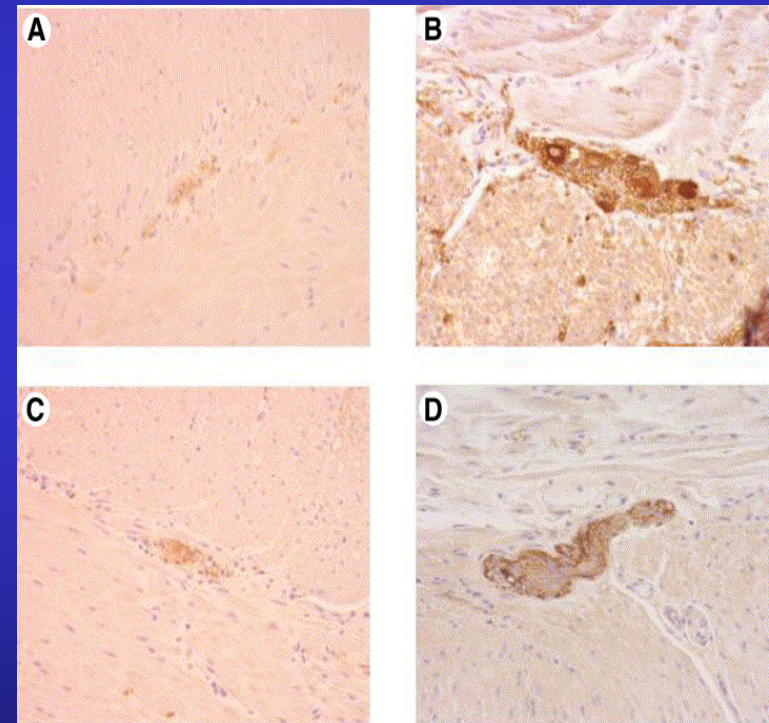
Complications of CIPO

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



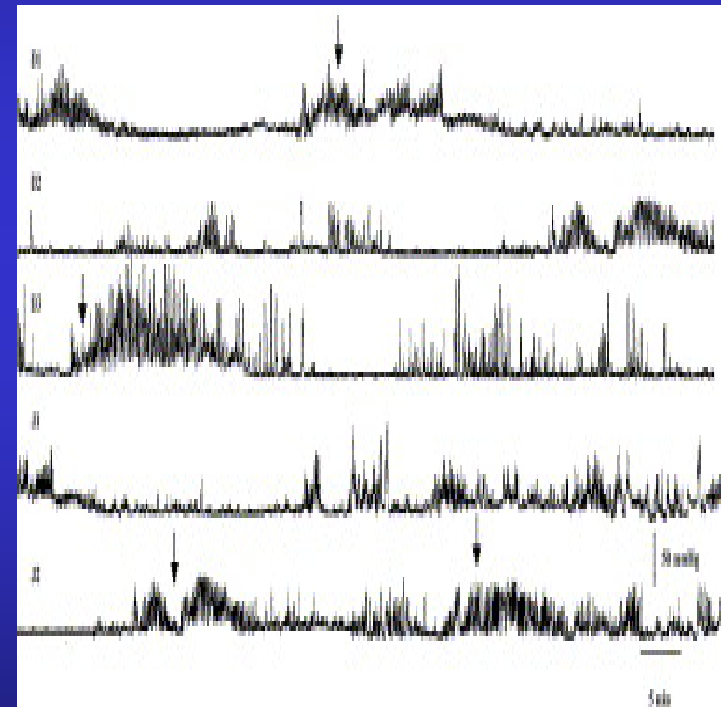
Pathophysiology of CIPO

- 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

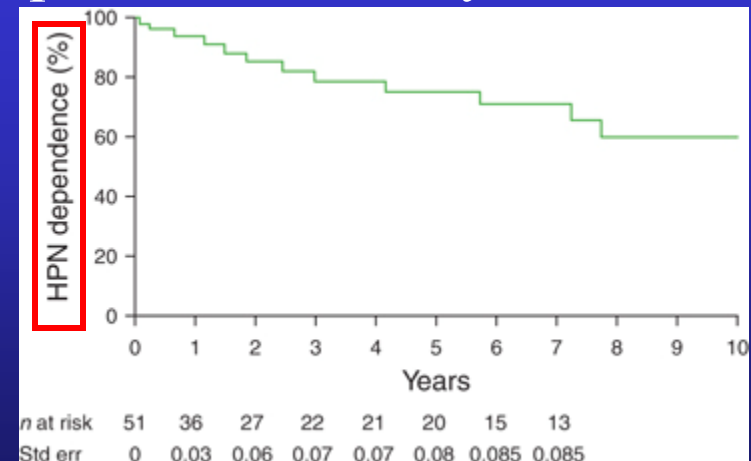
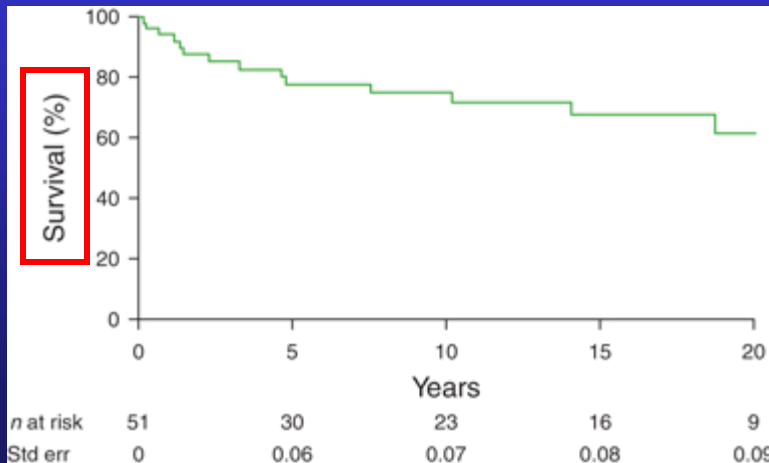


Natural History of CIPO

- 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

Natural History of CIPD in Patients on HPN

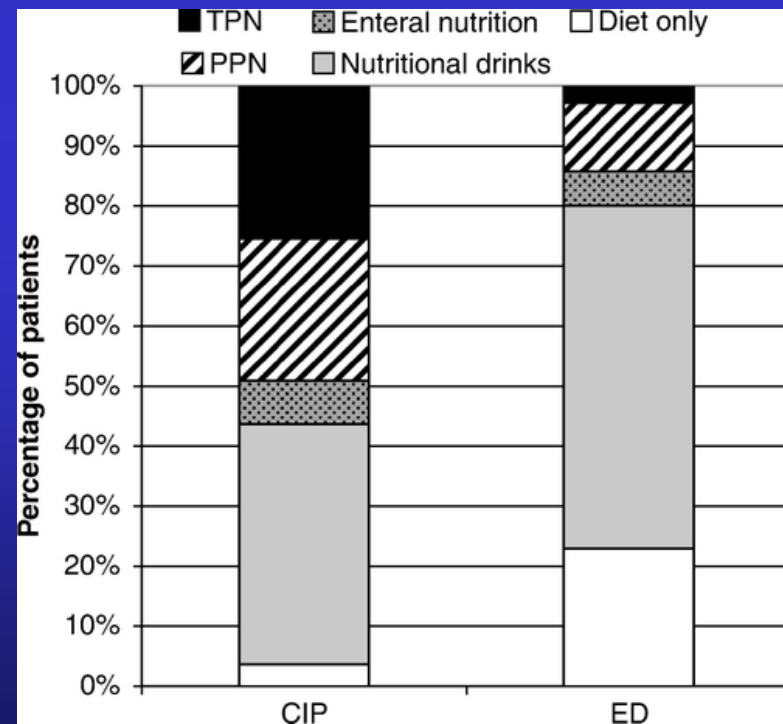
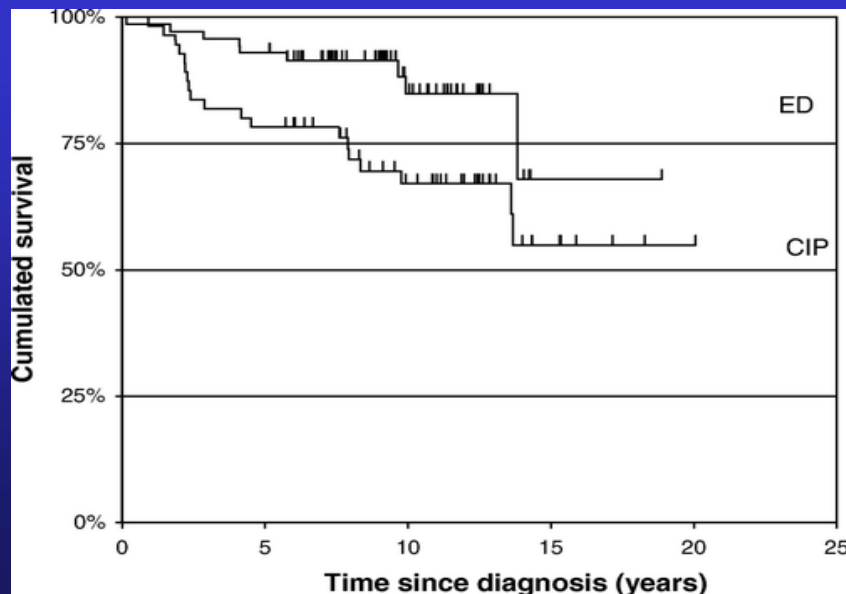
- 51 adults (18 male)
- Median age at symptom onset – 20 yrs (0-74)
- Mean follow up – 8.3 yrs (0-29)
- Mean # surgeries – 3 (SBS in 37%)
- Decreased mortality
 - Able to resume PO intake and symptom onset < 20 yrs



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

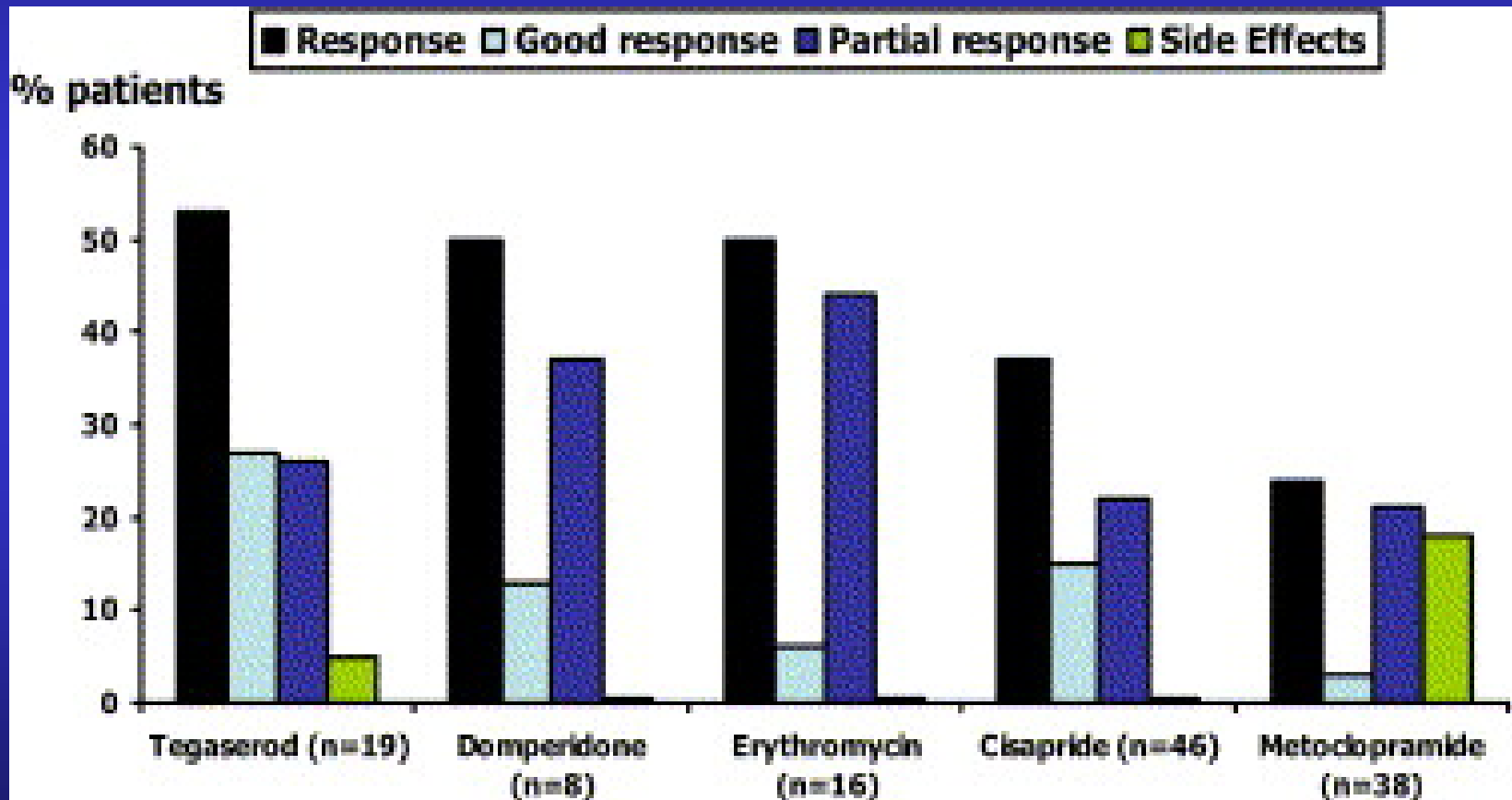
Dietary Modification

- 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

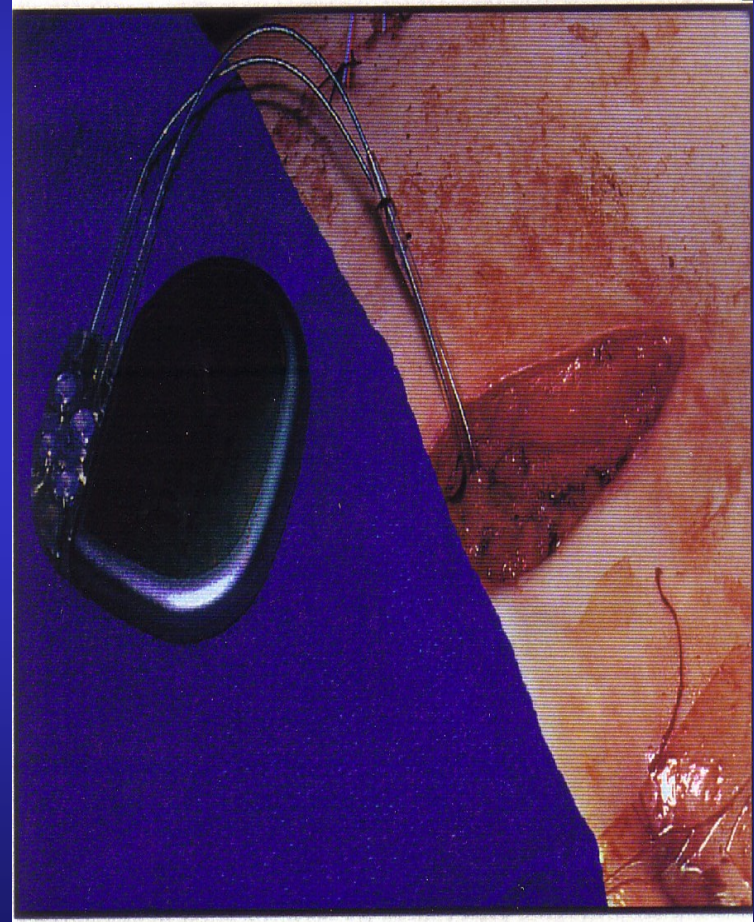
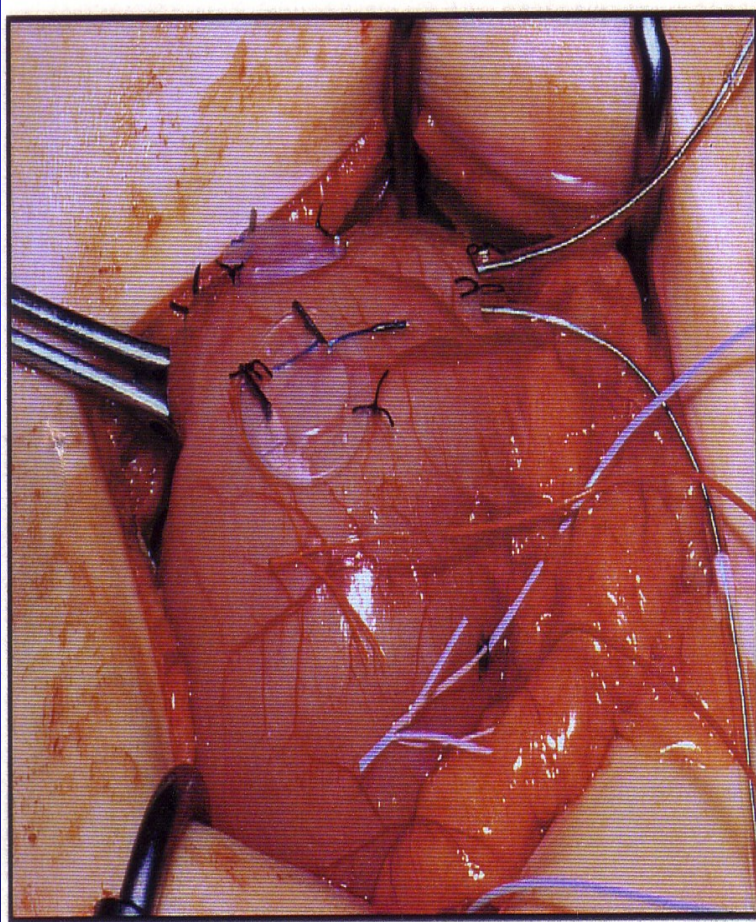
Response to Prokinetic Agents in CIPO



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

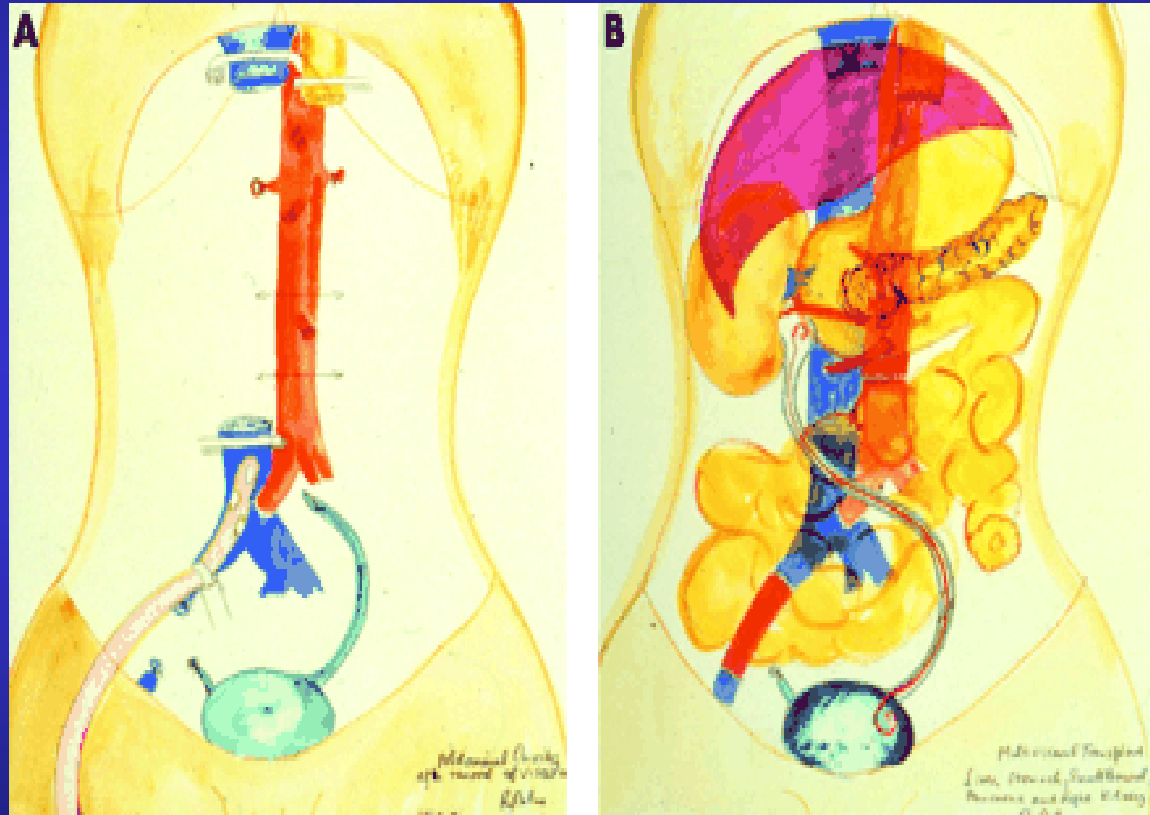
Electrical Stimulation



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% \leq 18 yrs of age
- More isolated bowel transplants in adults
- More combined bowel/liver transplants in peds

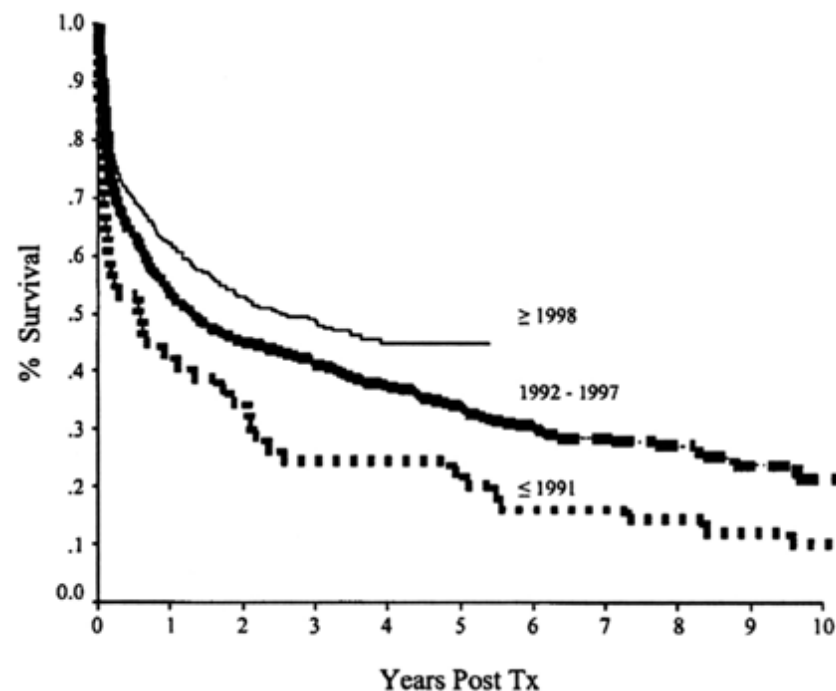
Intestinal Transplant Registry

Indications

- Pediatric
 - SBS
 - Gastroschisis (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%)

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%



	0	1	3	5	7	9
≥ 1998	641	290	101	16		
1992 - 1997	299	158	122	101	42	18
≤ 1991	49	21	12	11	8	6

Annals of Surgery • Volume 241, Number 4, April 2005

Intestinal Transplantation Registry

Outcomes (1985-2003)

- 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)

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