CELIAC DISEASE AND GLUTEN SENSITIVITY: IS WHEAT OUR ENEMY?

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GLUTEN RELATED DISORDERS

• CELIAC DISEASE
  GLUTEN ATAXIA, DERMATITIS HERPETIFORMIS

• WHEAT ALLERGY

• GLUTEN SENSITIVITY (NON-CELIAC)

GLUTEN RELATED DISORDERS

• General public and food industry have developed great interest in gluten

• >>>> medical community
- Analysis of NHANES data
- CD overall 0.71% (95% CI 0.58 – 0.86%)
- Among whites 1.01% (95% CI 0.78 – 1.31%)
- Only 17% with CD were diagnosed

Increasing Prevalence of Celiac Disease

Positive: +TTG, +EMA
PATHOPHYSIOLOGY OF CELIAC DISEASE

- Man was fully evolved when wheat was domesticated 11,000 years ago
- Gliadin is incompletely digested by gastric, duodenal, and pancreatic secretions in humans
- Leaving toxic epitopes, especially a 33 mer
- Enters lamina propria incites an immune response in some individuals

PATHOGENESIS OF CELIAC DISEASE

- Genetic factors
  - HLA DQ2/8
- Environmental factors
  - Autoantibodies (tTG, EMA)
  - Gastrointestinal and systemic manifestations
  - Intraepithelial lymphocytosis + villous atrophy

**Gluten**

**Epithelium**

- Innate response
- Lamina propria adaptive response

**Environment**

- ENDOSTATIC MANIFESTATIONS

ACG 2015 Annual Postgraduate Course
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ENVIRONMENTAL FACTORS – THE SWEDISH EPIDEMIC

- Celiac disease in childhood and adulthood
  - breast feeding (?)  NO
  - timing of gluten introduction  NO
  - cesarean section - elective
  - GI infections (rotavirus, Campylobacter)
  - season of birth
  - antibiotic use
  - iron supplements in pregnancy
  - PPI use
  - H. pylori (protective)

NOT CLEAR WHY CD CAN OCCUR AT ANY AGE
**CELIAC ANTIBODY TESTS**

- **GLIADIN PEPTIDE**: sensitive and specific
dGP IgG&IgA
- **TISSUE TRANSGLUTAMINASE IgA**
- **ENDOMYSIAL**: sensitive and very specific, but costly and observer dependent
- **MAINSTAY OF TESTING IS tTg IgA**
- **SERONEGATIVE CELIAC DISEASE OCCURS**

**PATHOLOGY-THE GOLD STANDARD**

- **Marsh I, II**
- **subtotal**
- **Villous atrophy (Marsh IIIa, b, c)**
- **partial**
- **total**
PRESENTATION OF CELIAC DISEASE (ADULTS)

Diarrhea (36%)
Incidental at EGD (4%)
Screening (8%)
Bone disease (5%)
Anemia (13%)
Other (20%)

N = 1499

DIAGNOSIS OF CELIAC DISEASE
why the underdiagnosis?

Patient
Case Finder
Endoscopist
Pathologist
ROLE OF THE ENDOSCOPIST

• Guidelines: need 4 – 6 biopsies
• Need biopsies of bulb – 1 or 2

ULTRA SHORT CELIAC DISEASE
when the bulb is the only site involved
• One biopsy per passage of forceps

Rostom A et al. Gastroenterology. 2006
Pais et al GIE 2008
Lebwohl et al GIE 2011
Latorre GIE 2015
Sanders DDW 2015

NON CELIAC GLUTEN SENSITIVITY

• PWAGs (People Who Avoid Gluten)
• Self diagnosis
• Analysis of NHANES data reveals it to be as common as celiac disease (0.8%)
• Compared to celiac disease
  blacks > whites (1.2% vs 0.7%)
PWAGS

- Other food avoidances: 52% (Dairy 59%, Soy 25%)
- Alternative Diagnoses: 38%
  - Small Intestinal Bacterial Overgrowth: 50%
  - Fructose Intolerance: 16%
  - Lactose Intolerance: 9%
  - Other food intolerances: 9%
  - Microscopic Colitis: 9%
  - Gastroparesis: 3%
  - Pelvic Floor Dysfunction: 3%

BEWARE OF THE ORTHORECTIC!!

Tavakkoli, DDS 2013

Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial

- Gluten sensitive IBS patients, n= 34
- Celiac disease while eating gluten was excluded
No Effects of Gluten in Patients With Self-Reported Non-Celiac Gluten Sensitivity After Dietary Reduction of Fermentable, Poorly Absorbed, Short-Chain Carbohydrates

JESSICA R. BIESEKERSKI,1,2 SIMONE L. PETERS,2 EVAN D. NEWNHAM,1 OURANIA ROSELLA,2 JANE G. MUIR,1 and PETER R. GIBSON2

1Department of Gastroenterology, Eastern Health Clinical School, Monash University, Box Hill, Victoria, Australia and 2Department of Gastroenterology, Centre Clinical School, Monash University, The Alfred Hospital, Melbourne, Victoria, Australia
A Controlled Trial of Gluten-Free Diet in Patients With Irritable Bowel Syndrome-Diarrhea: Effects on Bowel Frequency and Intestinal Function

Mara I. Vazquez-Roque, 1,2 Michael Camilleri, 1 Thomas Smyrk, 3 Joseph A. Murray, 1 Eric Maretta, 1 Jessica O'Neill, 1 Paula Carlson, 1 Jesse Lamson, 1 Denise Janzow, 1 Deborah Eckert, 1 Diane Burton, 1 and Alan B. Zimmeister 1

B

Gluten free diet

Gluten containing diet

Mean Bowel

Baseline

On diet

Open symbols: HLA DQ2/8 –ve
NON-CELIAC GLUTEN SENSITIVITY

- Exists (self diagnosis + non traditional practitioners)
- Mechanism unclear – gluten, permeability
- Some other component of gluten containing foods or wheat (ATIs)
- FODMAPs *Fermentable, Oligo-, Di-, Mono-saccharides And Polyols*
- About one third of GS actually are GS

ATHLETES AND THE GF DIET

*Exploring the Popularity, Experiences and Beliefs Surrounding Gluten-Free Diets in Non-Coeliac Athletes.*

Lis D, Stellingwerff T, Shing CM, Ahuja K DK, Fell J.
School of Human Life Sciences, University of Tasmania, Launceston, Tasmania, Australia.

- n=910, 18 Olympians, 41% of non-celiac athletes were on a GFD, 50%-100% of the time
- 13% for treatment of reported medical conditions
- 57% self-diagnosing their gluten sensitivity
  Due to perceived health benefits and increase in energy
GLUTEN FREE DIET

• Not necessarily healthy
• Low in fiber, B vitamins, and iron
• Concern about heavy metals
• Patients should be advised to diversify diet

• For the bulk of us gluten is not the enemy
• DEVELOPMENT OF NON-DIETARY THERAPIES FOR CD
Overview

- Review the clinical features and epidemiology of microscopic colitis
- Diagnostic criteria for MC
- Discuss treatment options
Clinical Features

Case Report

• 65 F with chief complaint diarrhea
• Onset 10 wk ago, slowly progressive
• 3-5 watery BM/d, 1-2 over night
• Mild pain relieved after BM, mucus but no blood
• Has lost 10 pounds
Points to Consider

• How likely does she have MC?
• Does she have IBS?
• What additional history do you want?
• Does she need colonoscopy?

Clinical Features

• Chronic watery diarrhea
• 50+% have abdominal pain, mild weight loss
• Autoimmune associations common, sprue
• Overlap with symptoms of IBS
  • 50-70% in Olmsted County
  • 28-65% in analysis of RCTs
• Association with NSAIDs and other meds

1) Limsui IBD 2007  2) Madish World J Gastro 2005
Predictors of MC vs. IBS

- Older age
- Female gender
- Shorter duration of diarrhea
  - 44-46% of patients with MC had less than 12 weeks of symptoms

1) LimSui IBD 2007  2) Abboud IBD 2013

Microscopic Colitis vs. Functional Diarrhea or IBS

Macaigne G, Am J Gastro 2014
Clinical Features

- Two subtypes
  - Collagenous and Lymphocytic colitis
- Very similar clinically and histologically
- Unclear if distinct or parts of a spectrum
Celiac sprue

- 1/3 of patients with sprue have MC-like changes on colon biopsies\(^1\),\(^2\)
- Sprue found in 2-13% or more of MC\(^3\)\(^-\)\(^6\)
- Celiac serologies may be less sensitive in MC\(^7\)
- Consider sprue if steatorrhea, iron deficiency, non-response to MC medications

7) Fine AJG 2000

Epidemiology
**Epidemiology**

- 7-20% of chronic watery diarrhea
- Incidence ~5-10/100,000 each
- Most common in elderly
- Female predominance (CC > LC in most)

**Age- and Gender-specific Incidence Rates Olmsted County, MN**

![Incidence rate graph](image_url)
Incidence of Microscopic colitis, Olmsted County 1985-2011

Case Report

- PMH: HTN, ↑cholesterol, GERD
- Meds: Olmesartan, simvastatin, omeprazole
- Denies aspirin, NSAID use
- FHx: No IBD, celiac sprue, colon cancer
Points to Consider

• Thoughts?
• Plan?

Pathophysiology

• Abnormal fluid/electrolyte secretion/absorption
• Bile acid malabsorption
• Abnormal collagen synthesis/degradation
• Infection
• Autoimmunity
• Reaction to luminal antigen
  • NSAIDs and other drugs
**Drug-induced Microscopic colitis**

- **High level evidence**
  - acarbose, aspirin, NSAIDs, PPI, SSRI, ticlopidine

- **Intermediate level evidence**
  - carbamazepine, flutamide, lisinopril, simvastatin

Beaugerie and Pardi APT 2005

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**Drug-induced Microscopic colitis**

- **Collagenous colitis**
  - Associated with NSAID, SSRI

- **Lymphocytic colitis**
  - B-blockers, SSRI, statins, bisphosphonates
  - not NSAID

- **Watery diarrhea**
  - SSRI, statins

Fernandez-Banares Am J Gastro 2007
**Drug-induced Microscopic colitis**

- Danish population-based retrospective study
- 3474 CC and 2277 LC diagnosed 2005-2011
- 100 matched controls per case
- PPI, NSAID, statin, SSRI use a/w CC and LC
- PPI and SSRI a/w diarrhea
- Adjusting for a/w diarrhea weakened a/w MC but still PPI:CC and SSRI:LC

**Case Report**

- Medications stopped for 6 weeks without improvement
- Does she need a colonoscopy?
- If has colonoscopy, does she need biopsies?
Diagnosis

• Does she need a colonoscopy?
  • Needs age appropriate colon cancer screening

• What about just for evaluation of diarrhea?
  • Has weight loss
  • Otherwise might consider empiric antidiarrheals
  • If she had recent colonoscopy, flex sig is sufficient in ~90%

• If has colonoscopy, does she need biopsies?
Predicting MC in Patients with Chronic Diarrhea

- Age >50, female, PPI and NSAID use, weight loss, absence of abdomen pain all a/w likelihood of MC on bx
- Combining these factors predicted MC with sensitivity 90-94%
- Avoided unnecessary bx in 45-49% of patients w/o MC

Case Report

- Loperamide up to 16 mg/d, no improvement
- Colonoscopy: Grossly normal
- Biopsies: next slide
Treatment
Bismuth

Bismuth Subsalicylate: Open-Label Study

- 13 patients newly dx (7 CC, 6 LC)
- BiSS 262 mg tablets, 8 daily, for 8 weeks
- Response 92%
- Mean time to response 2 weeks
- 75% maintained remission for 7-28 months

Fine and Lee, Gastroenterology 1998;114:29-36
Open-Label Bismuth: Clinical Results

Stool Frequency
5.3/day to 1.6/day

Stool Consistency

Fecal Weight
557 g/d to 274 g/d

Fine and Lee, Gastroenterology 1998;114:29-36

Open-Label Bismuth: Histology Results

Histopathology Score (0-10)
8.3 to 3.1

Fine and Lee, Gastroenterology 1998;114:29-36
**Bismuth Subsalicylate: RCT**

- N=14, 9 tabs/d x 8 weeks vs. placebo
- Response 100% vs. 0%
- BMs: 7.5/d to 2/d in BiSS; no $\Delta$ placebo
- Histology: improved in 6/7 BiSS, 1/6 placebo
- Relapse 25%, all retreated
- Placebo patients received BiSS: 5/6 improved
- No stats

Fine et al, DDW abstract (Gastro 1999;116:A880)

**Open Label Bismuth (Preliminary)**

- N=64 (25% of total), 52% LC, 48% CC
- 6-9 tabs/d x 8 weeks
- Complete response 48%
- Partial response 32%
- No response 20%
- Dose response: Remission 63% with 9 tabs, 35% with 6-8 tabs

Gentile N, et al. DDW 2015
## Open Label Bismuth (Preliminary)

Response by severity

<table>
<thead>
<tr>
<th>Daily BMs</th>
<th>None</th>
<th>Partial</th>
<th>Complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>7%</td>
<td>23%</td>
<td>69%</td>
</tr>
<tr>
<td>5-10</td>
<td>25%</td>
<td>36%</td>
<td>39%</td>
</tr>
<tr>
<td>&gt;10</td>
<td>40%</td>
<td>20%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Gentile N, et al. DDW 2015

## Mesalamine
Mesalamine +/- cholestyramine

- N=64, randomized but unblinded
- 2.4 gm/d +/- cholestyramine
- Remission 85% in LC (+ or – cholestyramine)
- CC: 73% w/o vs. 100% with cholestyramine

Calabrese J Gastro Hep 2007

Mesalamine Open-label Study

- N=35
- ~3 gm/day
- Remission
  - 83.3% in LC
  - 35.3% in CC (p=0.005)

Fernandez-Banares, Am J Gastro 2003
Open Label Treatment Responses

Complete and Partial Response

<table>
<thead>
<tr>
<th>Colitis type (N)</th>
<th>1LC (170)</th>
<th>2LC (199)</th>
<th>3CC (163)</th>
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<tbody>
<tr>
<td>Antidiarrheals</td>
<td>73%</td>
<td>70%</td>
<td>71%</td>
</tr>
<tr>
<td>Bismuth</td>
<td>73</td>
<td></td>
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<tr>
<td>Cholestyramine</td>
<td>65</td>
<td>57</td>
<td>59</td>
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<tr>
<td>5-ASA</td>
<td>42</td>
<td>37</td>
<td>35</td>
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<tr>
<td>Steroids</td>
<td>87</td>
<td>88</td>
<td>82</td>
</tr>
</tbody>
</table>

1) Pardi Am J Gastro 2002  
2) Olesen Gut 2004  
3) Bohr Gut 1996

Mesalamine RCT

• Collagenous colitis, N = 92

• Budesonide 9 mg/d vs. mesalamine 3 g/d vs. placebo

• Mesalamine no better than placebo
  • Remission (≤ 3 BM/d): 44% vs 60%
  • Remission (Hjortswang): 32% vs 38%
  • Histology 45% vs 50%

Miehlke Gastroenterology 2014;146:1222
Budesonide

Budesonide Placebo Controlled Trials

- 4 RCTs in collagenous, 2 in lymphocytic
- 9 mg/d x 6-8 weeks, +/- taper
- Response 57-100% (~85%) vs. 12-40%
- Relapse ~80%

Budesonide Induction in Collagenous Colitis: Cochrane Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Budesonide</th>
<th>Placebo</th>
<th>Peto OR</th>
<th>Weight</th>
<th>Peto OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>or sub-category</td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
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<tr>
<td>Baert 2002</td>
<td>8/11</td>
<td>3/12</td>
<td>25.04</td>
<td>6.23</td>
<td>[1.29, 30.92]</td>
</tr>
<tr>
<td>Bondenup 2003</td>
<td>10/10</td>
<td>2/10</td>
<td>21.13</td>
<td>23.73</td>
<td>[4.15, 135.72]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>47</td>
<td>47</td>
<td>100.00</td>
<td>12.32</td>
<td>[5.53, 27.48]</td>
</tr>
</tbody>
</table>

Total events: 38 (Budesonide), 8 (Placebo)
Test for heterogeneity: Chisq = 1.25, df = 2 (P = 0.54), P = 0%
Test for overall effect: Z = 6.14 (P < 0.0001)


Budesonide Induction in Lymphocytic Colitis

- N = 42
- 9 mg/day vs placebo

Case Report

- Bismuth subsalicylate, 3 TID for 6 weeks, no better
- Budesonide 9 mg/d, sx better after 4 days, resolved after 1 week
- D/C after 8 weeks
- 3 weeks later, symptoms return
Points to Consider

• What is going on?
• Does she need repeat colonoscopy with biopsies?
• Treatment?

Natural History of Steroid-treated MC

• 80 patients rx with steroids
  • 50% LC, 50% CC
  • Prednisone 21%, budesonide 79%
  • Remission 76%, response 20%
  • Recurrence 70%
• Remission: 83% vs 53% (p = 0.02)
• Recurrence: HR 0.38 (95% CI 0.18-0.85)

Gentile, Pardi Am J Gastro 2013
Budesonide Maintenance in Collagenous Colitis

- Two RCTs (N=82), 9 mg/d x 6 wks, remission 87-96%
- Budesonide 6 mg/d or placebo x 6 mo
- Relapse: 13-23% budesonide, 61-88% placebo

Bonderup Gut 2009
Miehlke Gastroenterology 2008

Budesonide Maintenance in Collagenous Colitis: Cochrane Meta-Analysis

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Budesonide n/N</th>
<th>Placebo n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
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<tbody>
<tr>
<td>Bonderup 2008</td>
<td>13/17</td>
<td>2/17</td>
<td>18.40 [3.82, 155.45]</td>
<td>81.60</td>
<td>5.31 [1.50, 18.84]</td>
</tr>
<tr>
<td>Miehlke 2008</td>
<td>17/23</td>
<td>8/23</td>
<td></td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td>40</td>
<td>40</td>
<td>160.00 [3.13, 84.37]</td>
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<tr>
<td>Total events: 30 (Budesonide), 10 (Placebo)</td>
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</tr>
<tr>
<td>Test for heterogeneity: CH² = 1.77, df = 1 (P = 0.19), P = 43.8%</td>
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<tr>
<td>Test for overall effect: Z = 4.20 (P &lt; 0.0001)</td>
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</tbody>
</table>

Favors placebo Favors budesonide

Points to Consider

• What do you monitor for with long term budesonide?
  • Steroid related side effects
• What dose do you use?
  • Lowest effective dose
• Any special instructions?
  • Avoid grapefruit, Echinacea, P450 drugs
• Alternative treatments?
Azathioprine for Microscopic Colitis

- 9 patients (2.3%), 8 CC, 1 LC
- Steroid dependent, refractory, or intolerant
- Median dose 2 mg/kg/d, f/u 26 months
- 7 tapered off steroids, no-mild symptoms
- 1 intolerant to steroids responded
- 1 non-responder: colectomy


Azathioprine for Microscopic Colitis

- 46 patients (32 CC, 14 LC)
- Mostly budesonide dependent, some intolerant (11%)
- Remission: 28%
- Intolerant: 67%
- Non-response: 4%
- 13 intolerant pts → 6-MP, 46% remission

Munch APT 2013
Methotrexate in Collagenous Colitis?

- N=19, med dose 7.5-10 mg/wk
- Response complete in 74%, partial in 11%
- But: N=9, 15 mg/wk SQ, ↑ 25 mg/wk after 6 wks if no response
- D/C due to side effects in 4
- In remaining 5, remission 0%

1) Riddell, J Gastro Hep 2007
2) Munch Clin Exp Gastro 2013

Anti-TNF in Microscopic Colitis

- N = 4 (of 372 pts, 1.1%) treated with infliximab
- Response after one dose
- 3 switched to adalimumab (2 allergic rxn, 1 loss of response)
- 3 maintained response thru 1 year
- 1 lost response to ADA → colectomy

Esteves J Crohns Colitis 2011
**Anti-TNF in Microscopic Colitis**

- N = 3 with CC refractory to budesonide and MTX
  - Adalimumab 160/80/40
  - 2 responded
  - 1 d/c after 2\textsuperscript{nd} dose (n/v, abdo pain)

_Archives of Disease in Childhood_ 2012

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**Recommended Treatment Approach**

- **D/C NSAIDs, other drugs**
- **Antidiarrheals**
- **Bismuth subsalicylate**
- **Budesonide**
- **Azathioprine/6-MP/(MTX)**
- **Anti-TNF**
- **Bile salt binder**
- **Prednisone?**
- **Surgery**

Mild to moderate: D/C NSAIDs, other drugs
Moderate to severe: Surgery

_Archives of Disease in Childhood_ 2012
Summary

• Incidence of MC appears to have stabilized
• Consider celiac disease
• Consider drug-induced MC
• Treat with bismuth or budesonide
  • Right dose and right duration
• Maintenance therapy with budesonide is often required
  • Monitor for steroid side effects

Thank you
CASE

- 47 y.o. male, lawyer
- Inflammatory/fistulizing Crohn’s Disease
- Multiple small bowel resections
- 100 cm jejunum to transverse colon remaining
- On parenteral nutrition for 32 years
- Course complicated by:
  - line infections
  - decreasing venous access
  - abnormal liver tests
Etiology of SBS

<table>
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<tr>
<th>University of Chicago</th>
<th>University of Nebraska</th>
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<tr>
<td>Radiation</td>
<td>Crohn's</td>
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<td>13%</td>
<td>44%</td>
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<td>Ischemia</td>
<td>Crohn's</td>
</tr>
<tr>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>Post-op</td>
<td>Ischemia</td>
</tr>
<tr>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
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<tr>
<td></td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>Post-op</td>
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<tr>
<td></td>
<td>35%</td>
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</table>

Thompson et al. JPEN 2015:DOI

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Rapid Dehydration output > 2 L/day

Must Know:
- Resection site
- Extent

Residual health

Length of Small Bowel
~ 600 cm
Small Bowel Response to Resection: Adaptive Dilation

Normal Bowel

Short Bowel

Slows Transit

Intestinal Adaptation

Stimulators of Hyperplasia

Luminal Factors
Nutrients
Non-nutrients
Secretions
- pancreatic
- biliary

Local Factors
Trefoil peptides
Prostaglandins
Polyamines

Hormones & Peptides
Enteroglucagon
Growth hormone
Gastrin, EGF, GLP-2
IGF-1, TGFα, IL11

↑ Nutrient/Fluid Absorption
Short Bowel Syndrome

Clinical Consequences

- Diarrhea / steatorrhea
- Dehydration
- Weight loss
- Manifestations of vitamin and mineral deficiencies

Risks of resection:

<100 cm bile-salt diarrhea
- cholestyramine tx

>100 cm fat malabsorption
- vit A, D, E, K, LCFA + B12
- bone disease
- oxalate stones

Large fluid losses

All nutrients malabsorbed

Rapid transit
Reconnect Colon when Possible

Messing et al. Gastroenterology 1999;117:1043
Short Bowel Syndrome

Basics of Management

• Block endogenous secretions
  - Proton Pump Inhibitor
  - Try octreotide if > 3 L/day output
• Slow motility to improve contact time
  - Loperamide, diphenoxylate
  - Liquid opiate
• Diet – multiple small meals, ORS
  - Jejunostomy (high salt, nutrient dense)
  - Colon present (low fat, low oxalate)
• Supplement vitamin/minerals
  - Vitamin B12 and fat-solubles, Ca, Zn, Mg
• Monitor wt, hydration, bone, stones, vit/minerals
  - Life-long

Parenteral Nutrition

- Dextrose
- Lipids
- Amino acids

Electrolytes & minerals
Vitamins
Trace elements

TPN
**Ethanol line locks decrease infection**

**Oliveira et al. Pediatrics 2012;129:318**

**Badia-Tahull et al. Nutrition 2015;31:1109**

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<table>
<thead>
<tr>
<th></th>
<th><strong>Home Parenteral Nutrition</strong></th>
<th><strong>Small Bowel Transplant</strong></th>
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<tbody>
<tr>
<td><strong>1 yr survival</strong></td>
<td>89%</td>
<td>78%</td>
</tr>
<tr>
<td><strong>5 yr survival</strong></td>
<td>75%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Morbidity</strong></td>
<td>line infection, liver disease, osteoporosis</td>
<td>rejection, GVHD, infection, lymphoma</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td>60-70% good</td>
<td>80-90% good at 6mo</td>
</tr>
<tr>
<td><strong>Long Term Cost</strong></td>
<td>$70-120,000/yr</td>
<td>$332,827/person/yr</td>
</tr>
</tbody>
</table>

Howard Gastroenterology 2006;130:S52
Abu-Elmagd Gastroenterology 2006;130:S132
Smith et al. OPTN/SRTR Am J Transplant 2014;1:97
Short Bowel Syndrome
Other Therapies

• Growth Hormone
  - conflicting results
  - ? main effect on colon
  - side effects (edema, arthralgia, sleep)
  - contraindications (infection, cancer)

• Night-time G tube feeding

• Bowel lengthening surgeries
  - mainly in children
  - Bianchi, STEP
Serial Transverse Enteroplasty (STEP)

Outcomes
• 16 children
• increased length 80 to 110 cm
• 60% tapered off EN/PN
• less favorable in gastroschisis

Novel Drug - Short Bowel Syndrome

Clinical Observation
• Gleeson 1971, Stevens 1984
  - glucagon-secreting tumor alters SB structure
  - glucagonoma syndrome and giant duodenal villi

Basic Science
• Drucker 1996 (Proc Natl Acad Sci 93:7911)
  - glucagon-like peptide 2 (GLP-2)
  - induced intestinal epithelial cell proliferation

Translational Human Pilot Study
• Jeppesen 2001 (Gastroenterology 120:806)
  - GLP2 increased absorption/decreased ostomy output

Stevens. Gut 1984;25:784
Teduglutide is a Novel GLP-2 Analogue

GLP-2 (short-acting)

HADGSFSDEMNTILDNLAARDFINWLIQTKITD
HGDGSFSDEMNTILDNLAARDFINWLIQTKITD

Teduglutide

Teuscher, Jeppesen, Mortensen et al 2005
Teduglutide Clinical Trials - Summary

• Safe (0.03 - 0.15 mg/kg SQ daily)
• PRCT in SBS, 83 pts, extended 52 wks
• Results:
  - increased villous height, crypt depth
  - increased absorption, lean body mass
  - decreased outputs
  - decreased PN needs in 68%, some stopped or day off PN (dose 0.05 mg/kg/day)
• Side effects: stoma hyperplasia, abd pain, inj site pain
• FDA approved, no contraindications, no time limit
  - Short bowel, PN/IV fluid-dependent, on optimal care

Jeppesen et al Gut 2005;54:1224 and 2011;60:902

Real Time Experience in Short Bowel/Intestinal Failure

Pt #1 – Case Patient
• Off PN after 32 yrs!
• Line free – dove into swimming pool
• Sleeps through the night
Teduglutide
Unanswered Questions

• ? Needed daily
• ? Cancer risk
  - colon cancer
  - pancreatic cancer
• ? What about the small stuff
  - vitamin/mineral/essential fatty acid deficiencies
• Will price come down
  - novel, orphan drug

Short Bowel Syndrome Management
Take Home Points

• Know site/length resected to guide therapy
• Optimize medical regimen
  - multiple small meals, ORS
  - block acid, slow motility
  - extensive resections likely need PN
• Teduglutide (GLP-2 analogue) improves uptake
• Consider lengthening surgery if dilated bowel
• Small Bowel Transplant when
  - loss of vascular access, liver disease
• Monitor for nutrient deficiencies, bones, stones