Fire in the Gut I
Nutritional Modulation of IBS

KU Clinical Nutrition Seminar 10-12-2012

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Objectives

• To examine the pathophysiology of IBS
• To outline some of the root cause of IBS
• To review the evidence for using nutraceutical supplements in treating IBS
• To discuss the role of diet in IBS
“The gut is important in medical research not just for problems with the digestive system but for the rest of the body” Jay Pasricha
Rome III Criteria for IBS

- A chronic disorder characterized by **abdominal pain or discomfort associated with disordered defecation**
- Symptoms should have developed at least 6 months before the patient first presents for formal evaluation
- Abdominal pain or discomfort should be present at least 3 days per month for 3 months and should be associated with two or more of the following:
  - improvement with defecation,
  - onset associated with a change in stool frequency, and/or
  - onset associated with a change in stool form.
The Pathogenesis of IBS


Genetic Predisposition

Development Of IBS

Manifestation Of IBS symptoms

Stress

History Of Abuse

Infection/Inflammation/SIBO

Environmental Influences

Parental Modeling

Other Factors

Anxiety

Somatization

Depression

Poor Coping Skills

Stress
BRAIN:
- SSRI's / TCA
- Cognitive Behavioural Therapy (CBT)

GUT:
- 5 ASA
- Sodium Cromglycate
- CRH antagonist
- Probiotics
Use of Nutritional Products in IBS

- 40% of patients with IBS claim to have used some form of herbal medication in USA
- Herbal products and nutraceuticals are the most frequent form of alternative therapies used in IBS

Emerging Nutritional Approaches to IBS in 2012

- Supplements
- Gut Microbiome
- Diet
Herbs Commonly Used for Gastrointestinal Disease

<table>
<thead>
<tr>
<th>Herb</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginger</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Berberine</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>Peppermint</td>
<td>IBS</td>
</tr>
<tr>
<td>Licorice</td>
<td>PUD</td>
</tr>
<tr>
<td>Mastic Gum</td>
<td>PUD</td>
</tr>
<tr>
<td>Tannins</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Flaxseed</td>
<td>Constipation</td>
</tr>
</tbody>
</table>
Treatment of IBS with TCM

# Traditional Chinese Herbal Medicine to Treat IBS

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Treatment Description</th>
<th>Duration</th>
<th>Outcome Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bensoussan et al (1998)</td>
<td>116</td>
<td>All IBS forms, determined by Rome criteria (not specified)</td>
<td>R,D,P</td>
<td>Standard TCM mixture of 33 herbs (n=43), individualized formula (n=38), or placebo (n=35), 5 capsules tid for 16 weeks. Significant reduction in bowel symptom scores and increase in QOL for individual preparation and standard TCM compared to placebo</td>
</tr>
<tr>
<td>Wang et al (2008)</td>
<td>24</td>
<td>All IBS forms, evaluation not specified</td>
<td>R,non-D,P</td>
<td>24 g Shugan Jianpi granules tid, 24 g Shugan Jianpi granules plus 15 g Smecta® tid, or cognitive therapy and lactein treatment as standard care for 2 weeks. Significant reduction in serotonin positive cells in both Shugan Jianpi groups compared to standard care</td>
</tr>
<tr>
<td>Leung et al (2006)</td>
<td>119</td>
<td>IBS-D, IBS determined by Rome II criteria</td>
<td>R,D,P</td>
<td>See Table 7 for daily dose of each herb (n=60) or placebo (n=59) for 8 weeks. No significant improvement in SF-36 or global symptoms compared to placebo</td>
</tr>
</tbody>
</table>

R: Randomized, D: Double-blind, P: Placebo-controlled

# Iberogast

<table>
<thead>
<tr>
<th>Plant (Latin name)</th>
<th>Herb-Extract ratio (alcoholic extracts)</th>
<th>In 100 mL Iberogast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitter candytuft (<em>Iberis amara</em>)</td>
<td>1:1.5-2.5</td>
<td>15.0 mL</td>
</tr>
<tr>
<td>Angelica root (<em>Angelica archangelica</em>)</td>
<td>1:2.5-3.5</td>
<td>10.0 mL</td>
</tr>
<tr>
<td>Chamomile flowers (<em>Matricaria recutita</em>)</td>
<td>1:2.5-4.0</td>
<td>20.0 mL</td>
</tr>
<tr>
<td>Caraway fruits (<em>Carum carvi</em>)</td>
<td>1:2.5-3.5</td>
<td>10.0 mL</td>
</tr>
<tr>
<td>Milk thistle fruits (<em>Silybum marianum</em>)</td>
<td>1:2.5-3.5</td>
<td>10.0 mL</td>
</tr>
<tr>
<td>Lemon balm leaves (<em>Melissa officinalis</em>)</td>
<td>1:2.5-3.5</td>
<td>10.0 mL</td>
</tr>
<tr>
<td>Peppermint leaves (<em>Mentha x piperita</em>)</td>
<td>1:2.5-3.5</td>
<td>5.0 mL</td>
</tr>
<tr>
<td>Celandine (<em>Chelidonium majus</em>)</td>
<td>1:2.5-3.5</td>
<td>10.0 mL</td>
</tr>
<tr>
<td>Licorice root extract (<em>Glycyrrhiza glabra</em>)</td>
<td>1:2.5-3.5</td>
<td>10.0 mL</td>
</tr>
</tbody>
</table>

Iberogast Improves IBS

- **Commercially available herbal preparation STW 5):**
  - bitter candytuft
  - chamomile flower
  - peppermint leaves
  - caraway fruit
  - licorice root
  - lemon balm leaves
  - celandine herbs
  - angelica root
  - milk thistle fruit.

- **Research herbal preparation (STW 5-II):**
  - bitter candytuft
  - chamomile flower
  - peppermint leaves
  - caraway fruit
  - licorice root
  - lemon balm leaves.

Iberogast
Improves IBS Symptoms


- Irritable bowel syndrome (IBS) symptom score (s.d.) for the various treatment groups at baseline and after 2 and 4 weeks of treatment. Intention-to-treat population.
  - \*P = 0.0033,  \( P = 0.0035 \), \**P = 0.0009\) and \( P = 0.0005 \) vs. placebo.
- STW 5, commercially available herbal preparation (nine plant extracts)
- STW 5-II, research herbal preparation (six plant extracts)
- BCT, bitter candytuft mono-extract.

Level A
Iberogast
Improves IBS Pain

Abdominal Pain score (s.d.) for the various treatment groups at baseline and after 2 and 4 weeks of treatment. Intention-to-treat population.

*P = 0.0085,  P = 0.0006, **P = 0.001 and  
P = 0.0003 vs. placebo.

STW 5, commercially available herbal preparation (nine plant extracts)

STW 5-II, research herbal preparation (six plant extracts)

BCT, bitter candytuft mono-extract.

Iberogast Improves IBS: Mechanisms of Action

STW 5 plant extracts:

anti-inflammatory, anti-ulcerogenic, carminative and antibacterial properties.

*In vitro* studies:

> 10-fold higher affinity of STW 5 to both M3 and 5-HT4 receptors than to 5-HT3 receptors.

Celandine herb and chamomile flowers are selective to 5-HT4 receptors
Licorice root to 5-HT3 receptors

Simmen U, Kelber O, Jäggi R, Büter B, Okpanyi SN, Weiser D. Relevance of the herbal combination of STW 5 for its binding affinity to the muscarinic M3 receptor. 2003; (Suppl. 1A): R22
## Pharmacological Effects of Iberogast

<table>
<thead>
<tr>
<th>Symptoms / Botanical</th>
<th>Acid secretion</th>
<th>Inflammation</th>
<th>Oxidative processes</th>
<th>Hypomotility</th>
<th>Hypermotility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peppermint leaf extract</td>
<td>W</td>
<td>S</td>
<td>S</td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td>Chamomile flower extract</td>
<td>S</td>
<td>W</td>
<td>M</td>
<td>M</td>
<td>S</td>
</tr>
<tr>
<td>Licorice root extract</td>
<td>W</td>
<td>S</td>
<td>W</td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td>Angelica root extract</td>
<td>M</td>
<td>W</td>
<td>M</td>
<td>N</td>
<td>S</td>
</tr>
<tr>
<td>Caraway fruit extract</td>
<td>M</td>
<td>S</td>
<td>W</td>
<td>N</td>
<td>W</td>
</tr>
<tr>
<td>Milk thistle fruit extract</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td>Melissa leaf extract</td>
<td>M</td>
<td>M</td>
<td>S</td>
<td>N</td>
<td>W</td>
</tr>
<tr>
<td>Celandine herb extract</td>
<td>N</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>N</td>
</tr>
<tr>
<td>Bitter candytuft extract</td>
<td>M</td>
<td>S</td>
<td>W</td>
<td>M</td>
<td>W</td>
</tr>
</tbody>
</table>

N = No effect, W = Weak effect, M = Moderate effect, S = Strong effect

Peppermint

- Animal model studies demonstrate:
  - relaxation effect on gastrointestinal (GI) tissue
  - analgesic and anesthetic effects in the central and peripheral nervous system
  - immunomodulating actions
  - chemopreventive potential
- Blocks calcium channels in gastrointestinal smooth muscle to produce spasmolytic response

Forest plot of randomized controlled trials of peppermint oil versus placebo in the irritable bowel syndrome.

Events are number of patients with either global symptoms of irritable bowel syndrome or abdominal pain unimproved or persistent after treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Relative risk (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lech 1988\textsuperscript{29}</td>
<td>10/23</td>
<td>18/24</td>
<td></td>
<td>23.82</td>
<td>0.58 (0.34 to 0.98)</td>
</tr>
<tr>
<td>Liu 1997\textsuperscript{30}</td>
<td>14/55</td>
<td>34/55</td>
<td></td>
<td>25.33</td>
<td>0.41 (0.25 to 0.68)</td>
</tr>
<tr>
<td>Capanni 2005\textsuperscript{32}</td>
<td>18/91</td>
<td>56/87</td>
<td></td>
<td>29.58</td>
<td>0.31 (0.20 to 0.48)</td>
</tr>
<tr>
<td>Cappello 2007\textsuperscript{31}</td>
<td>10/28</td>
<td>19/29</td>
<td></td>
<td>21.27</td>
<td>0.55 (0.31 to 0.96)</td>
</tr>
<tr>
<td>Ford, A. C et al. BMJ 2008;337:a2313</td>
<td>197</td>
<td>195</td>
<td></td>
<td>100.00</td>
<td>0.43 (0.32 to 0.59)</td>
</tr>
</tbody>
</table>

Total (95% CI) 197 195
Total events: 52 (treatment), 127 (control)
Test for heterogeneity: $\chi^2 = 4.36$, df=3, P=0.23, $I^2 = 31.1\%$
Test for overall effect: $z = 5.39$, P<0.001

Favours treatment

Favours control
Efficacy of Therapies for IBS

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Trials</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peppermint Oil</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Hycosamine</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Alosetron</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Tegaserod</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>TCAs</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

*BMJ 2008;337: a2313*
# Other Herbal Therapies for IBS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample size</th>
<th>Sample characteristics</th>
<th>Study design</th>
<th>Dose of active</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bundy et al (2004)</td>
<td>207</td>
<td>All IBS forms, IBS determined by Rome II criteria</td>
<td>R, non-D, non-P</td>
<td>2 doses, 72 mg (1 tablet) or 144 mg (2 tablets) daily</td>
<td>8 weeks</td>
<td>Significant improvement in IBS QOL at end of trial compared to baseline for both treatment groups</td>
</tr>
<tr>
<td><strong>Artichoke leaf extract</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walker et al (2001)</td>
<td>279</td>
<td>All IBS forms, meeting at least 3 out of 5 Rome II criteria</td>
<td>R, non-D, non-P</td>
<td>320 mg artichoke leaf extract per cap; 2 caps tid w/ meals</td>
<td>6 weeks</td>
<td>Significant reduction of IBS-related symptoms evaluated on a Likert scale at end of study compared to baseline</td>
</tr>
<tr>
<td>Bundy et al (2004)</td>
<td>208</td>
<td>All IBS forms, meeting at least 3 out of 5 Rome II criteria</td>
<td>R, non-D, non-P</td>
<td>320 mg (1 capsule) or 640 mg (2 capsules) of 1:5 artichoke leaf extract daily</td>
<td>8 weeks</td>
<td>Significant reduction in NDI QOL score at end of trial compared to baseline</td>
</tr>
</tbody>
</table>

Melatonin

Sleep

Depression

Anxiety

IBS???
Is Melatonin involved in IBS?

JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2009, 60, Suppl 3, 67-70

Fig. 1. The 6-sulphatoxy melatonin/creatinine (SMLT/crea) (ng/mg) excretion in healthy controls and patients with irritable bowel syndrome (IBS) with constipation (C-IBS) and diarrhea (D-IBS).
Melatonin improves bowel symptoms in females with IBS: a double-blind placebo-controlled study

Table 4. Changes in mean scores of individual IBS symptoms after treatment with either melatonin or placebo

<table>
<thead>
<tr>
<th>Scores</th>
<th>Melatonin</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in mean (s.d.) abdominal pain scores</td>
<td>1.17 (1.2)</td>
<td>0.47 (1.6)</td>
<td>0.045</td>
</tr>
<tr>
<td>Change in mean (s.d.) abdominal distension scores</td>
<td>0.62 (0.6)</td>
<td>0.12 (0.7)</td>
<td>0.019</td>
</tr>
<tr>
<td>Change in mean (s.d.) abnormal sensation of defecation scores</td>
<td>1.15 (1.1)</td>
<td>0.24 (1.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Change in mean (s.d.) stool consistency scores</td>
<td>0.45 (0.7)</td>
<td>0.41 (0.9)</td>
<td>0.9</td>
</tr>
<tr>
<td>Change in mean (s.d.) frequency of defecation scores</td>
<td>-0.7 (1.1)</td>
<td>-0.9 (1.4)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

3 mg/D x 8wk, washout, cross over

Lu WZ. Aliment Pharmacol Ther 2005 Nov 15;22;10:927-34.
Emerging Complementary Approaches to IBS in 2012

- Supplements
- **Gut Microbiome**
- Elimination Diets
Post-Infectious IBS

• May be responsible for up to 30% of all IBS
• Has been reported following food borne illness, traveler’s diarrhea and outbreaks of *Salmonella*, *Shigella*, *Giardia*, *Campylobacter*
• Risk factors: long duration of diarrhea (>3 weeks), female, psychological factors: anxiety, depression
• IBS may begin up to 4-6 mo. after exposure
Factors Activating Mucosal Immune System in IBS

- Food Antigens
- Bacteria
- EC Cell

- Plasma Cell
- Dendritic Cell
- Activated T Cells
- Mast Cell

- Stress hormones
Post-infectious IBS

- Increased numbers of T lymphocytes and mast cells lying in the lamina propria
- Release of tryptase and histamine excite visceral sensory afferent nerves leading to gut sensory and motor dysfunction


Red stains tryptase in mast cells
Green stains neuronal specific enolase
Altered Gut Microbiome in IBS

• associated specific microbiome signatures with pediatric IBS (Saulnier et.al. Gastro 2011;141:1782-91)

• microbiota of IBS had a 2-fold increased ratio of the Firmicutes to Bacteroidetes ($P = .0002$). Correlation analysis of the microbial groups and IBS symptom scores indicated the involvement of several groups of Firmicutes and Proteobacteria in the pathogenesis of IBS (Rajilic-Stojanivoc Gastro 2011;141:1782-91)
Altered Gut Microbiome in IBS

- A major functional dysbiosis was observed in constipated-IBS gut microbiota, reflecting altered intestinal fermentation.
- Sulphate-reducing population increased in the gut of C-IBS and were accompanied by alterations in other microbial groups.
- This could be responsible for changes in the metabolic output and enhancement in toxic sulphide production which could in turn influence gut physiology and contribute to IBS pathogenesis. (Chassard et.al. Aliment Pharmacol Ther. 2012 Apr;35(7):828-38)
Distribution of Intestinal Bacterial Flora in Normal Gut and in Small Intestinal Bacterial Overgrowth

Origin of gas/bloating of IBS patients with SIBO

Relationship of SIBO to IBS

Proportion meta-analysis plot [random effects]

- Pimentel 2000: 0.78 (0.71, 0.83)
- Nucera 2005: 0.65 (0.55, 0.75)
- Madrid 2007: 0.76 (0.70, 0.82)
- Parodi 2007: 0.50 (0.41, 0.59)
- Bratten 2008: 0.14 (0.09, 0.20)
- Carrara 2008: 0.43 (0.35, 0.52)
- Combined: 0.54 (0.32, 0.76)

Level A

Source: Clinical Gastroenterology and Hepatology 2009; 7:1279-1286 (DOI:10.1016/j.cgh.2009.06.031)
Among patients who had IBS without constipation, treatment with rifaximin for 2 weeks provided significant relief of IBS symptoms, bloating, abdominal pain, and loose or watery stools. (Funded by Salix Pharmaceuticals; ClinicalTrials.gov numbers, NCT00731679 and NCT00724126.)

Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation

Mark Pimentel, M.D., Anthony Lembo, M.D., William D. Chey, M.D., Salam Zakko, M.D., Yehuda Ringel, M.D., Jing Yu, Ph.D., Shadreck M. Mareya, Ph.D., Audrey L. Shaw, Ph.D., Enoch Bortey, Ph.D., and William P. Forbes, Pharm.D., for the TARGET Study Group*

ABSTRACT

BACKGROUND
Evidence suggests that gut flora may play an important role in the pathophysiology of the irritable bowel syndrome (IBS). We evaluated rifaximin, a minimally absorbed antibiotic, as treatment for IBS.

METHODS
In two identically designed, phase 3, double-blind, placebo-controlled trials (TARGET 1 and TARGET 2), patients who had IBS without constipation were randomly assigned to either rifaximin at a dose of 550 mg or placebo, three times daily for 2 weeks, and were followed for an additional 10 weeks. The primary end point, the proportion of patients who had adequate relief of global IBS symptoms, and the key secondary end point, the proportion of patients who had adequate relief
Rifaximin Improves IBS

**Figure 4.** Percentage of Patients with Adequate Relief of Global IBS Symptoms in the TARGET 1 and TARGET 2 Studies Combined.

Adequate relief was defined as self-reported relief from symptoms for at least 1 week of every 2-week period. The P value was calculated on the basis of a longitudinal data analysis with the use of a generalized-estimating-equation model, with fixed effects of treatment, analysis center, and week. Similar figures for the individual TARGET 1 and TARGET 2 trials are shown in the Supplementary Appendix.
Treatment Options for SIBO

The goal is to treat the underlying cause(s), eradicate the bacterial overgrowth, and nutritional support

- Antibiotic therapy
- Prokinetic agents
- Herbs (berberine, oregano oil, wormwood)
- Diet
- Enzymes/HCl
**Benefits of Probiotics in IBS**

**potential mechanisms of action**

<table>
<thead>
<tr>
<th>IBS</th>
<th>Probiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Post-infectious</td>
<td>– Elimination of pathogens</td>
</tr>
<tr>
<td>– Bacterial overgrowth</td>
<td>– Modulate composition of intestinal flora</td>
</tr>
<tr>
<td>– Qualitative alterations in fecal flora</td>
<td>– Reduce bacterial fermentation</td>
</tr>
<tr>
<td>– Increased bacterial fermentation</td>
<td>– Reduce pathogen-related inflammation</td>
</tr>
<tr>
<td>– Proinflammatory cytokines</td>
<td></td>
</tr>
</tbody>
</table>

* Effect on bloating most consistent effect of probiotics
## Meta-analysis for Probiotic Use in IBS

**Review:** probiotics for IBS
**Comparison:** 01 probiotics vs placebo
**Outcome:** 01 risk of IBS not improving

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Lactobacillus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nobae 00</td>
<td>21/30</td>
<td>25/30</td>
<td></td>
<td>12.86</td>
<td>0.84 (0.63 to 1.12)</td>
</tr>
<tr>
<td>Niedziewski 01</td>
<td>11/20</td>
<td>17/20</td>
<td></td>
<td>9.91</td>
<td>0.65 (0.42 to 1.00)</td>
</tr>
<tr>
<td>Sinn 08</td>
<td>4/20</td>
<td>13/20</td>
<td></td>
<td>4.11</td>
<td>0.31 (0.12 to 0.78)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>70</td>
<td>70</td>
<td></td>
<td>26.88</td>
<td>0.64 (0.41 to 1.02)</td>
</tr>
<tr>
<td>Total events:</td>
<td>36 (treatment), 55 (control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 5.48$, df = 2 (p = 0.06), $I^2 = 63.5%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 1.87$ (p=0.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim 03</td>
<td>8/12</td>
<td>8/13</td>
<td></td>
<td>7.51</td>
<td>1.08 (0.60 to 1.95)</td>
</tr>
<tr>
<td>Tsuchiya 04</td>
<td>7/34</td>
<td>30/34</td>
<td></td>
<td>6.44</td>
<td>0.23 (0.12 to 0.48)</td>
</tr>
<tr>
<td>Kajander 05</td>
<td>21/52</td>
<td>34/51</td>
<td></td>
<td>10.91</td>
<td>0.61 (0.41 to 0.89)</td>
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<tr>
<td>Drouault-Holowacz 08</td>
<td>33/53</td>
<td>31/53</td>
<td></td>
<td>12.37</td>
<td>1.06 (0.79 to 1.45)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>151</td>
<td>151</td>
<td></td>
<td>37.23</td>
<td>0.66 (0.36 to 1.20)</td>
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<tr>
<td>Total events:</td>
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<tr>
<td>Test for heterogeneity: $\chi^2 = 20.92$, df = 3 (p = 0.0001), $I^2 = 85.7%$</td>
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<tr>
<td>Test for overall effect: $Z = 1.36$ (p = 0.17)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>03 Bifidobacterium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long 06</td>
<td>13/30</td>
<td>21/30</td>
<td></td>
<td>9.31</td>
<td>0.62 (0.39 to 0.99)</td>
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<tr>
<td>Whorwell 06</td>
<td>143/270</td>
<td>54/92</td>
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<td>14.35</td>
<td>0.90 (0.74 to 1.11)</td>
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<td>Subtotal (95% CI)</td>
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<td>122</td>
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<td>23.66</td>
<td>0.80 (0.56 to 1.13)</td>
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<td>Total events:</td>
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<tr>
<td>Test for heterogeneity: $\chi^2 = 2.07$, df = 1 (p = 0.15), $I^2 = 51.7%$</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 1.29$ (p = 0.20)</td>
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<tr>
<td>04 Streptococcus</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Gade 89</td>
<td>20/32</td>
<td>19/22</td>
<td></td>
<td>12.23</td>
<td>0.72 (0.53 to 0.99)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>32</td>
<td>22</td>
<td></td>
<td>12.23</td>
<td>0.72 (0.53 to 0.99)</td>
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<tr>
<td>Total events:</td>
<td>20 (treatment), 19 (control)</td>
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<tr>
<td>Test for heterogeneity: not applicable</td>
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<td></td>
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<tr>
<td>Test for overall effect: $Z = 2.01$ (p = 0.04)</td>
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<td></td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
<td>0.71 (0.57 to 0.88)</td>
</tr>
<tr>
<td>Total events:</td>
<td>281 (treatment), 252 (control)</td>
<td></td>
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</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 28.33$, df = 9 (p = 0.0008), $I^2 = 68.2%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 3.12$ (p = 0.002)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

## Summary of Evidence for Nutritional-based Therapies for IBS

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>BODY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peppermint oil</td>
<td>2 meta-analyses of 5 and 4 RCTs</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Meta-analysis of 23 RCTs</td>
</tr>
<tr>
<td>Soluble fibre</td>
<td>Meta-analysis of 9 RCTs</td>
</tr>
<tr>
<td>Iberogast</td>
<td></td>
</tr>
<tr>
<td>Artichoke leaf extract</td>
<td>2 RCTs</td>
</tr>
<tr>
<td>Tumeric</td>
<td>1 RCT</td>
</tr>
</tbody>
</table>
Emerging Options for IBS

- Supplements
- Gut Microbiome
- Elimination Diets
> 60% IBS patients report worsening symptoms after meals, 28% within 15 minutes, 93% within 3 hours.
Food Reaction in Patients with IBS

• 25% of Us population claim and they have an adverse reaction to one or more foods
• IBS 32% claim they have an adverse reaction to a specific food
• Culprits:
  – Carbs
  – Allergens
  – Lactose, Fructose
  – FODMAPs
  – Gluten*

*3.6 of IBS patients have Celiac disease vs. 0.7% US population
Exclusion-Based Diets

• Based on Food Hypersensitivity Testing Dairy (IgG4, ALCAT, etc)
• Top 8 Food Allergens
• Carbs, Lactose, Fructose, FODMAPs, Gluten
• Caffeine, Additives, Amines
• Elimination Diet (suspected vs. restrictive)
Prevalence of Lactose Intolerance in IBS

IBS patients (n=251): 38%
Controls (n=174): 26%
Fructose and Fructans As Dietary Triggers for IBS symptoms

Food elimination based on IgG antibodies in irritable bowel syndrome: a randomized controlled trial.

# Results of Studies of Immunoglobulin G (IgG) Antibody-Elimination Diets for Irritable Bowel Syndrome (IBS).

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Subjects</th>
<th>Trial</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkinson et al(^{19}) 150 IBS</td>
<td>True diet vs sham 3 mo</td>
<td>True diet resulted in a 10% greater reduction in symptom score than the sham diet (P = .024), with this value increasing to 26% in fully compliant patients (P &lt; .001).</td>
<td></td>
</tr>
<tr>
<td>Zar et al(^{17}) 52 IBS-D, 32 IBS-C, 43 controls</td>
<td>IgG(_4) and IgE antibodies</td>
<td>IBS had significantly higher IgG(_4) titers to wheat (P &lt; .001), beef (P &lt; .001), pork (P &lt; .001), and lamb (P = .009) compared with controls. These differences were maintained across all 3 subgroups. Testing for IgE food antibodies was not helpful for IBS, except in a small subgroup of patients with diarrhea predominant-disease and atopy.</td>
<td></td>
</tr>
<tr>
<td>Drisko et al(^{18}) 15 IBS, refractory to medical therapy</td>
<td>Elimination-rotational diet, 6 mo</td>
<td>Baseline abnormalities were identified on serum IgG food and mold panels in 100% of the study subjects (P &lt; .005); significant improvements in stool frequency, pain, IBS-QOL.</td>
<td></td>
</tr>
<tr>
<td>Yang et al(^{22}) 55 IBS-D, 32 IBS-C, 18 controls</td>
<td>8-wk elimination diet</td>
<td>The positive rate of serum food-specific IgG antibodies was 63.5% in patients with IBS-D and 43.8% in IBS-C; improved IBS symptom relief.</td>
<td></td>
</tr>
<tr>
<td>Zuo et al(^{23}) 37 IBS, 20 controls</td>
<td>IgG(_4) antibodies</td>
<td>IBS patients had significantly higher titers of IgG antibody to crab (P = .000), egg (P = .000), shrimp (P = .000), soybean (P = .017), and wheat (P = .004) than controls. Serum IgG antibody titers to some common foods were increased in IBS patients compared with controls.</td>
<td></td>
</tr>
</tbody>
</table>

IBS-C; constipation-predominant IBS; IBS-D; diarrhea-predominant IBS; IgE, immunoglobulin-E; QOL, quality of life.
Very Low CHO Diet for IBS-D

- 15 females, mean age 46 yrs, BMI 32
- Dietary interventions:
  - 2 wks standard (55% CHO, 30% Fat, 15% Protein)
  - 4 wks VLC (51% Fat, 45% Protein, 4% CHO)
- Responder: Adequate relief of GI symptoms for 2/4 weeks
  - Responder rate = 13/13 (100%)
  - 10/13 (77%) improved 4/4 weeks
  - Improvements in stool frequency (p<0.001), consistency (p<0.001), pain (p<0.001), QoL (p=0.02)
  - Mean weight loss of 3.1 kg

Austin et al. *Clin Gastro Hepatol* 2009;7:706
Yield of Diagnostic Tests for Celiac Disease in Individuals With Symptoms Suggestive of Irritable Bowel Syndrome

Systematic Review and Meta-analysis

Alexander C. Ford, MBChB, MD, MRCP; William D. Chey, MD; Nicholas J. Talley, MD, PhD; Ashish Malhotra, MD; Brennan M. R. Spiegel, MD, MSHS; Paul Moayyedi, PhD, FRCP

Background: Individuals with irritable bowel syndrome (IBS) report abdominal pain, bloating, and diarrhea, symptoms similar to those in celiac disease. Studies suggest that the prevalence of celiac disease is increased in individuals with IBS; however, evidence is conflicting, and current guidelines do not always recommend screening for celiac disease in these individuals.

Methods: We conducted a systematic review and meta-analysis to estimate prevalence of celiac disease in unselected adults who met diagnostic criteria for IBS. MEDLINE (1950 to May 31, 2008) and EMBASE (1980 to May 31, 2008) were searched. Case series and control studies that used serologic tests for celiac disease were eligible for inclusion. Prevalence of positive serologic indications of celiac disease and biopsy-proved celiac disease were extracted and pooled for all IBS individuals and controls.

Results: Fourteen studies were identified comprising 4204 individuals, of whom 2278 (54%) met diagnostic criteria for IBS. Pooled prevalence of positive IgA-class antigliadin antibodies, either positive endomysial antibodies or tissue transglutaminase, and biopsy-proved celiac disease were 4.0% (95% confidence interval, 1.7-7.2), 1.63% (0.7-3.0), and 4.1% (1.9-7.0), respectively. Pooled odds ratios (95% confidence intervals) for positive IgA-class antigliadin antibodies, either positive endomysial antibodies or positive tissue transglutaminase, and biopsy-proved celiac disease in individuals with IBS were 4.03 (2.32-7.01), 4.03 (2.09-7.85), and 4.05 (2.03-8.06), respectively.

Conclusion: Prevalence of biopsy-proved celiac disease in cases meeting diagnostic criteria for IBS was more than 4-fold that in controls without IBS.

Arch Intern Med. 2009;169(7):651-658
Yield of Diagnostic Tests for Celiac Disease in Individuals With Symptoms Suggestive of Irritable Bowel Syndrome: Systematic Review and Meta-analysis

Gluten Sensitivity

• An adverse reaction occurring upon ingestion of gluten in patients who do not have celiac disease or wheat allergy and whose symptoms subside after gluten withdrawal’

• Much more commonly seen in adults than in children

• The definition is necessarily broad, as many clinical manifestations are attributed to gluten sensitivity, ranging from strictly gastrointestinal to extra-intestinal such as fatigue, headaches, joint pain….

Curr Gastroenterol Rep 2011 Jul 27
Gluten Sensitivity

• Up to 10% of the general population
• Encompasses a collection of medical conditions in which gluten leads to an adverse effect
• Can be clinically indistinguishable from celiac sprue but testing is negative or inconclusive
• Not associated with increased intestinal permeability
• Innate immunity markers TLR2 & FOXP3 altered in GS but not Celiac disease
• Improves with a gluten free diet

Is it IBS, Celiac Disease or Something in Between?

Gluten Sensitivity

**IBS symptoms**
- Motility/Visceral Sensation
- Brain-Gut Interactions
- Immune activation
- Altered Gut Microbiome
- Altered Permeability

**Spectrum of CD**
- Silent CD
- Latent CD
- CD & Complications
Participants received either gluten or placebo in the form of two bread slices plus one muffin per day with a gluten-free diet for up to 6 weeks. Of 19 patients (68%) in the gluten group, 13 reported that symptoms were not adequately controlled compared with 6 of 15 (40%) on placebo ($P=0.0001$; generalized estimating equation). On a visual analog scale, patients were significantly worse with gluten within 1 week for overall symptoms ($P=0.047$), pain ($P=0.016$), bloating ($P=0.031$), satisfaction with stool consistency ($P=0.024$), and tiredness ($P=0.001$).
Gluten Induces GI Symptoms

Our data confirm the existence of non-celiac WS as a distinct clinical condition. We also suggest the existence of two distinct populations of subjects with WS: one with characteristics more similar to CD and the other with characteristics pointing to food allergy.
Our results clearly showed that a relevant percentage — one third of our irritable bowel syndrome patients who underwent DBPC wheat challenge were really suffering from WS.

WS patients were characterized by frequent self-reported wheat intolerance and coexistent atopy and food allergy in infancy.

The main histological characteristic of WS patients was eosinophil infiltration of the duodenal and colon mucosa.
Food Reactions and IBS Summary

- Patients with IBS-D/M should be screened for celiac disease
- Expected US prevalence in IBS pts is ≤1% but likely varies based upon population genetics
- Lactose intolerance may be more common in IBS
- Clinical implications of CHO intolerance may be different in persons with than without IBS
- Food can affect GI function and sensation
- Mounting evidence suggests that dietary & lifestyle interventions can improve symptoms in a subset of IBS sufferers
Fiber
The Forgotten Factor

• Traditional treatment for IBS
• Type of fiber matters
  – Insoluble fiber such as wheat bran may exacerbate IBS symptoms
  – Soluble fiber (psyllium husk) more beneficial
• Gradual increase in fiber intake + fluids
Forest plot of randomized controlled trials of fibre versus placebo or low fibre diet in IBS

<table>
<thead>
<tr>
<th>Subcategory and study</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Relative risk (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bran</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Soltof 1976w7</td>
<td>17/32</td>
<td>12/27</td>
<td>6.19</td>
<td>1.20 (0.70 to 2.04)</td>
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<tr>
<td>Manning 1977w3</td>
<td>7/14</td>
<td>7/12</td>
<td>3.65</td>
<td>0.86 (0.42 to 1.74)</td>
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<tr>
<td>Kruis 1986w4</td>
<td>29/40</td>
<td>28/40</td>
<td>17.86</td>
<td>1.04 (0.78 to 1.37)</td>
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<tr>
<td>Lucey 1987w7</td>
<td>3/14</td>
<td>4/14</td>
<td>1.13</td>
<td>0.75 (0.20 to 2.75)</td>
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<td>Rees 2005w1</td>
<td>6/14</td>
<td>7/14</td>
<td>2.91</td>
<td>0.86 (0.39 to 1.91)</td>
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<td>Subtotal (95% CI)</td>
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<td>107</td>
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<td>1.02 (0.82 to 1.27)</td>
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Test for heterogeneity: $\chi^2=0.99$, df=4, $p=0.91$, $I^2=0$
Test for overall effect: $z=0.16$, $p=0.88$

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<td>Ritchie 1979w31</td>
<td>7/12</td>
<td>12/12</td>
<td>7.50</td>
<td>0.58 (0.36 to 0.94)</td>
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<td>Longstreth 1981w3</td>
<td>17/37</td>
<td>16/40</td>
<td>6.56</td>
<td>1.15 (0.69 to 1.92)</td>
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<tr>
<td>Arthurs 1983w5</td>
<td>11/40</td>
<td>14/38</td>
<td>4.26</td>
<td>0.75 (0.39 to 1.43)</td>
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<tr>
<td>Nilam 1984w5</td>
<td>13/21</td>
<td>21/21</td>
<td>13.54</td>
<td>0.62 (0.44 to 0.87)</td>
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<tr>
<td>Prior 1987w5</td>
<td>33/40</td>
<td>37/40</td>
<td>32.59</td>
<td>0.89 (0.75 to 1.05)</td>
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<td>Jailhal 1990w5</td>
<td>2/11</td>
<td>3/9</td>
<td>0.80</td>
<td>0.55 (0.11 to 2.59)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>161</td>
<td>160</td>
<td>65.24</td>
<td>0.78 (0.63 to 0.96)</td>
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Test for heterogeneity: $\chi^2=7.63$, df=5, $p=0.18$, $I^2=34.4$
Test for overall effect: $z=2.31$, $p=0.02$

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<tr>
<td>Fowile 1992w4</td>
<td>10/25</td>
<td>7/24</td>
<td>3.00</td>
<td>1.37 (0.62 to 3.01)</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>25</td>
<td>24</td>
<td>3.00</td>
<td>1.37 (0.62 to 3.01)</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect: $z=0.79$, $p=0.43$

Total (95% CI) | 300  
Total events: 155 (treatment), 168 (control)
Test for heterogeneity: $\chi^2=12.82$, df=11, $p=0.31$, $I^2=14.2$
Test for overall effect: $z=1.93$, $p=0.05$
FODMAPs & IBS

• Fermentable Oligo, Di, Monosaccharides And Polyols
• Family of poorly absorbed, short-chain carbohydrates
  – lactose,
  – fructose,
  – fructo-and galacto-oligosaccharides (fructans and galactans)
  – Polyols (sorbitol, mannitol, xylitol and maltitol)
• Highly fermentable in the presence of gut bacteria (SIBO)
GASTROENTEROLOGY

Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome

Derrick K Ong,*,† Shaylyn B Mitchell,*,† Jacqueline S Barrett,*,† Sue J Shepherd,*,† Peter M Irving,*,† Jessica R Biesiekierski,*,† Stuart Smith,† Peter R Gibson* and Jane G Muir*

*Department of Medicine, Eastern Health Clinical School, Monash University, and †School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Victoria, Australia

Key words
breath testing, carbohydrates, dietary therapy, FODMAPs, gastrointestinal symptoms, irritable bowel syndrome.

Accepted for publication 26 April 2010.

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Dr Jane Muir, Department of Medicine, Monash University, Level 1-5 Arnold St, Box Hill, Vic. 3128, Australia. Email: jane.muir@med.monash.edu.au

Conflicts of interest: S.J.S has published cookbooks directed towards issues of dietary fructan restrictions, fructose malabsorption and celiac disease. She has also published shopping guides for low FODMAPs and low fructose and fructan foods.

Abstract
Background and Aim: Reduction of short-chain poorly absorbed carbohydrates (FODMAPs) in the diet reduces symptoms of irritable bowel syndrome (IBS). In the present study, we aimed to compare the patterns of breath hydrogen and methane and symptoms produced in response to diets that differed only in FODMAP content.

Methods: Fifteen healthy subjects and 15 with IBS (Rome III criteria) undertook a single-blind, crossover intervention trial involving consuming provided diets that were either low (9 g/day) or high (50 g/day) in FODMAPs for 2 days. Food and gastrointestinal symptom diaries were kept and breath samples collected hourly over 14 h on day 2 of each diet.

Results: Higher levels of breath hydrogen were produced over the entire day with the high FODMAP diet for healthy volunteers (181 ± 77 ppm, 14 h vs 43 ± 18; mean ± SD P < 0.0001) and patients with IBS (242 ± 79 vs 62 ± 23; P < 0.0001), who had higher levels during each dietary period than the controls (P < 0.05). Breath methane, produced by 10 subjects within each group, was reduced with the high FODMAP intake in healthy subjects (47 ± 29 vs 109 ± 77; P = 0.043), but was not different in patients with IBS (126 ± 153 vs 86 ± 72). Gastrointestinal symptoms and lethargy were significantly induced by the high FODMAP diet in patients with IBS, while only increased flatus production was reported by healthy volunteers.

Conclusions: Dietary FODMAPs induce prolonged hydrogen production in the intestine
FODMAPs Pathology

Diagram showing the effects of dietary FODMAPs on physiological effects and symptom induction.

- **Diet**
  - Fructose
  - Fructans
  - Lactose
  - Galactans
  - Polyols

- **Physiological effects**
  - Osmotic load
    - ↑ water delivery
  - Rapidly fermentable substrate
    - ↑ rate of gas production

- **Symptom induction**
  - Motility change
  - Bloating
  - Pain/discomfort
  - Wind
Figure 2  Individual responses in breath hydrogen ($n = 15$ (irritable bowel syndrome [IBS]), $n = 14$ (healthy) shown as area-under-the-curve) to low and high FODMAP diets in healthy subjects and patients with IBS. Total breath hydrogen was significantly greater on the high FODMAP diet in both groups ($P < 0.0001$, paired t-test test). Outlier was
IBS Patients on High FODMAP Diet Produce Breath Methane

Figure 1  Profiles of breath hydrogen (n = 15 (irritable bowel syndrome [IBS]) and n = 14 (healthy controls), mean ± SEM) production over 14 h of each dietary period in healthy subjects and patients with IBS on high FODMAP diets (HFD) and low FODMAP diets (LFD). Total breath hydrogen was significantly greater on the HFD diet in both groups (P < 0.0001, paired t-test test). Patients with IBS produced significantly more breath hydrogen over the 14-h period than healthy controls during both the HFD (P = 0.039, unpaired t-test) and LFD (P = 0.025). One outlier from the healthy control group for breath hydrogen was removed (86ppm.14h [LFD] and 400ppm.14h [HFD]).  ●, Healthy—HFD;  ●, Healthy—LFD;  ■, IBS—HFD;  □, IBS—LFD.
Low FODMAP Diet Improves IBS Symptoms

Table 3  Symptom scores during the low and high FODMAPs diet for healthy subjects and patients with irritable bowel syndrome (IBS) during day 2 according to self-rating Likert scale where 0 = no symptoms, 1 = slight, 2 = moderate, 3 = severe

<table>
<thead>
<tr>
<th>Symptom(s)</th>
<th>Group</th>
<th>Number of subjects with symptom score (Likert scale)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low FODMAP diet</td>
<td>High FODMAP diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain/discomfort</td>
<td>Healthy</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>IBS</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal bloating</td>
<td>Healthy</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>IBS</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Excessive flatus</td>
<td>Healthy</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>IBS</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>Healthy</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>IBS</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Heartburn</td>
<td>Healthy</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>IBS</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Tiredness/lethargy</td>
<td>Healthy</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>IBS</td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>

Low FODMAP vs. Standard Diet for IBS

Top FODMAPs Rich-Foods

- Grains: wheat & rye
- Fruits: apples & pears
- Vegetables: onions
- Dairy: milk and soft cheeses (cottage/ricotta)
- Sweeteners: Agave, honey
- Other: High fructose corn syrup & polyols
<table>
<thead>
<tr>
<th>FODMAP</th>
<th>Fructose</th>
<th>Polyols</th>
<th>Lactose</th>
<th>Fructans and Galactans</th>
</tr>
</thead>
<tbody>
<tr>
<td>High FODMAP food sources</td>
<td>Apples, pears, watermelon, honey, fruit juices, dried fruits, high-fructose corn syrup</td>
<td>Sugar alcohols (sorbitol, maltitol, mannitol, xylitol, and isomalt), stone fruits, avocado, mushrooms, cauliflower</td>
<td>Milk (cow, goat, sheep), yogurt, soft cheeses (ricotta, cottage)</td>
<td>Wheat, rye, garlic, onions, artichokes, asparagus, inulin, soy, leeks, legumes, lentils, cabbage, Brussels sprouts, broccoli</td>
</tr>
<tr>
<td>Alternative lower FODMAP food sources</td>
<td>Citrus, berries, bananas, grapes, honeydew, cantaloupe, kiwifruit</td>
<td>Sweeteners, such as sugar, glucose, other artificial sweeteners not ending in “-ol” (Stevia)</td>
<td>Lactose-free dairy products, rice milk, hard cheeses</td>
<td>Starches, such as rice, corn, potato, quinoa. Vegetables, such as winter squash, lettuce, spinach, cucumbers, bell peppers, green beans, tomato, eggplant</td>
</tr>
</tbody>
</table>
Although the pathophysiology of visceral hypersensitivity is still unclear, two key factors have been identified as playing a major role in its modulation, namely peripheral corticotropin-releasing factor (CRF) and mast cells.
### Studies of Mast Cells in IBS

<table>
<thead>
<tr>
<th>No. of IBS</th>
<th>No. of control</th>
<th>Duodenum</th>
<th>Jejunum</th>
<th>Ileum</th>
<th>Colon</th>
<th>Significance</th>
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<tbody>
<tr>
<td>48</td>
<td>24</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+</td>
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<tr>
<td>50</td>
<td>21</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+</td>
<td>yes</td>
</tr>
<tr>
<td>41</td>
<td>48</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>yes</td>
</tr>
<tr>
<td>44</td>
<td>22</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+</td>
<td>yes</td>
</tr>
<tr>
<td>20</td>
<td>14</td>
<td>N/A</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
<td>yes</td>
</tr>
<tr>
<td>42</td>
<td>12</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+</td>
<td>yes</td>
</tr>
</tbody>
</table>

Asia Pac Allergy. 2011 Apr;1(1):36-42
Leaky Gut in Patients with Diarrhea-Predominant Irritable Bowel Syndrome and Inactive Ulcerative Colitis

Krisztina Gecse\textsuperscript{a}  Richárd Róka\textsuperscript{a}  Anita Annaházi\textsuperscript{a}  Ferenc Izbéki\textsuperscript{a}  László Pávics\textsuperscript{b}  Lionel Bueno\textsuperscript{c}  Titkos Zs.

\textsuperscript{a}First Department of Internal Medicine and \textsuperscript{b}Department of Gastroenterology, Semmelweis University, Budapest, Hungary; \textsuperscript{c}INRA, UMR 1054 INRA-El Purpan, Toulouse, France

Colonic permeability of IBS-D and inactive UC patients was significantly increased compared to controls (2.68 ± 0.35 and 3.74 ± 0.49 vs. 1.04 ± 0.18%; \textit{p} < 0.05, \textit{p} < 0.001). Colonic permeability of IBS-D patients correlated with stool frequency.
Leaky Gut in IBS-D

**Fig. 1.** 24-hour excretion of $^{51}$Cr-EDTA in subgroups of IBS and inactive UC patients compared to control subjects.

**Fig. 2.** Excretion of $^{51}$Cr-EDTA measured between 0 and 3 h after ingestion in subgroups of IBS and inactive UC patients compared to control subjects, which represents proximal small intestinal permeability.
Gut Permeability and Food Allergies

Clinical & Experimental Allergy
volume 41, issue 1, pages 20-28, 11 NOV 2010 DOI: 10.1111/j.1365-2222.2010.03639.x
Mucosal Permeability and Immune Activation as Potential Therapeutic Targets of Probiotics in Irritable Bowel Syndrome

Giovanni Barbara, MD, Lisa Zecchi, MS, Raffaella Barbaro, PhD, Cesare Cremon, MD, Lara Bellacosa, MD, Marco Marcellini, MD, Roberto De Giorgio, MD, PhD, Roberto Corinaldesi, MD, and Vincenzo Stanghellini, MD

Abstract: There is increasing evidence suggesting a critical role for the participation of the gut microbiota in the pathogenesis of irritable bowel syndrome (IBS). This process involves the interplay between luminal factors (eg, foods and bacteria residing in the intestine), the epithelial barrier, and the mucosal immune system. Decreased expression and structural rearrangement of tight junction proteins in the small bowel and colon leading to increased intestinal permeability have been observed, particularly in post-infectious IBS and in IBS with diarrhea. These abnormalities are thought to contribute to the outflow of antigens through the leaky epithelium, causing overstimulation of the mucosal immune system. Accordingly, subsets of patients with IBS show higher numbers and an increased activation of mucosal immunocytes, particularly mast cells. Immune factors, released by these cells, including proteases, histamine, and prostanoids, participate in the perpetuation of the permeability dysfunction and contribute to the activation of abnormal neural responses involved in abdominal pain perception and changes in bowel habits. All these mechanisms are enhanced by 10% to 15% in Europe and are believed to be the consequence of dysregulation of the brain-gut axis with both the central and peripheral mechanism involved. Luminal factors (eg, microbiota, food, and bile acids), increased intestinal permeability, and low-grade immune activation have been suggested as important players in the IBS pathophysiology in addition to the development of abdominal pain and changes in bowel habits. These abnormalities represent novel targets for therapies and nonpharmacological approaches. Probiotics are attractive therapeutic options for IBS given their safety, the paucity of side effects, and the numerous potentially beneficial effects on the above-mentioned pathophysiological targets. Here, we will briefly review novel mucosal targets for probiotic therapies in IBS.
Mucosal Permeability and Immune Activation as Potential Therapeutic Targets of Probiotics in Irritable Bowel Syndrome

“Decreased expression and structural rearrangement of tight junction proteins in the small bowel and colon leading to increased intestinal permeability have been observed, particularly in post-infectious IBS and in IBS with diarrhea. These abnormalities are thought to contribute to the outflow of antigens through the leaky epithelium, causing overstimulation of the mucosal immune system.

Accordingly, subsets of patients with IBS show higher numbers and an increased activation of mucosal immunocytes, particularly mast cells. Immune factors, released by these cells, including proteases, histamine, and prostanoids, participate in the perpetuation of the permeability dysfunction and contribute to the activation of abnormal neural responses involved in abdominal pain perception and changes in bowel habits. All these mechanisms represent new targets for therapeutic approaches in IBS.”
Mast Cell

Activating factors
- Intestinal permeability

Bacteria and biproducts
- Food allergies (IgE- & non-IgE-mediated)
- Neuropeptides
- Bile acids

Inflammatory mediators
- Histamine
- Tryptase
- Lipid mediators
- Cytokines

CNS
- Stress

ENS
- Altered gut secretion & motility

GI Pain
- CPPS

Pain
- Neural cross-talk

Corticotropin
- Releasing Factor
Carminative

A carminative is an herb that relieves flatulence and/or GI cramping.
## Food Carminatives

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Ingredient</th>
<th>Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allspice*</td>
<td>Cloves</td>
<td>Marjoram</td>
</tr>
<tr>
<td>Anise seed</td>
<td>Coriander</td>
<td>Nutmeg</td>
</tr>
<tr>
<td>Asafoetida</td>
<td>Cumin*</td>
<td>Onion</td>
</tr>
<tr>
<td>Basil</td>
<td>Dill*</td>
<td>Oregano</td>
</tr>
<tr>
<td>Bergamot</td>
<td>Epazote</td>
<td>Peppermint*</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Fennel*</td>
<td>Rosemary</td>
</tr>
<tr>
<td>Caraway*</td>
<td>Ginger *</td>
<td>Sage*</td>
</tr>
<tr>
<td>Cardamom</td>
<td>Lemon balm*</td>
<td>Saffron</td>
</tr>
<tr>
<td>Cinnamon</td>
<td>Licorice</td>
<td>Sarsaparilla</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spearmint</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyme</td>
</tr>
</tbody>
</table>

BMC Complement Altern Med. 2007 Feb 7;7:4
Nutritional Tools for Your IBS Patient

- Anti-anxiety Herbs
- Anti-microbials for SIBO
- Artichoke leaf extract
- Elimination Diet
- Fiber
- FODMAP restricted diet
- Melatonin
- Peppermint Oil
- Probiotics
- Turmeric
# CAM Evidence Ratings for IBS

## Table 2. Summary of Complementary Therapies and Current Evidence Ratings for Irritable Bowel Syndrome

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Application</th>
<th>Evidence Rating (Strength of Recommendation Taxonomy Criteria)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive behavior therapy</td>
<td>See text</td>
<td>A</td>
</tr>
<tr>
<td>Hypnosis</td>
<td>See text</td>
<td>B</td>
</tr>
<tr>
<td>Elimination diet</td>
<td>Remove foods in Table 1 for 2 wk</td>
<td>B</td>
</tr>
<tr>
<td>Probiotics</td>
<td><em>Bifidobacterium infantis</em> (1×10⁸ colony-forming units daily) VSL#3</td>
<td>B</td>
</tr>
<tr>
<td>Prebiotics</td>
<td>Food sources include bananas, artichokes, onions, asparagus, and chicory</td>
<td>C</td>
</tr>
<tr>
<td>Fiber</td>
<td>Guar gum (5 g/d)</td>
<td>A</td>
</tr>
<tr>
<td>L-glutamine</td>
<td>5 g twice daily</td>
<td>C</td>
</tr>
<tr>
<td>Peppermint</td>
<td>0.2-0.4 mL enteric-coated capsules 3 times daily</td>
<td>B</td>
</tr>
<tr>
<td>Zinc</td>
<td>37.5 mg/d</td>
<td>C</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>400 mg 3-4 times daily</td>
<td>B</td>
</tr>
</tbody>
</table>

*From Ebell et al. A indicates recommendation based on consistent and good-quality patient-oriented evidence; B, recommendation based on inconsistent or limited-quality patient-oriented evidence; and C, recommendation based on consensus, usual practice, opinion, disease-oriented evidence, and case series for studies of diagnosis, treatment, prevention, or screening.*
The practice of medicine is an art, not a trade; a calling, not a business; a calling in which your heart will be exercised equally with your head. Often the best part of your work will have nothing to do with potions and powders, but with the exercise of an influence of the strong upon the weak, of the righteous upon the wicked, of the wise upon the foolish.

~ Sir William Osler, The Three Great Lessons of Life
INTEGRATIVE GASTROENTEROLOGY

GERARD E. MULLIN, MD

GASTROINTESTINAL AND LIVER DISEASE NUTRITION DESK REFERENCE

Edited by Gerard E. Mullin, Lauren E. Mattei, and Melissa Palmer

THE INSIDE TRACT

YOUR GOOD GUT GUIDE TO GREAT DIGESTIVE HEALTH

Foreword by Andrew Weil, MD

Gerard E. Mullin, MD, and Kathie Madonna Swift, MS, RD, LDN
Fire in the Gut II
Nutritional Modulation of IBD

KU Clinical Nutrition Seminar 10-12-2012

Gerard E. Mullin MD
Director of Integrative GI Nutrition Services
Johns Hopkins Hospital
600 N. Wolfe Street CARN 464B
Baltimore MD 21205
Learning Objectives

• Apply knowledge of inflammatory antecedents, triggers, and mediators to create effective, individualized treatment plans for patients with digestive dysfunction.

• Be able to appropriately prescribe diet, nutraceuticals, and botanicals to decrease inflammation and oxidative stress in the digestive tract.
Outline

• Anti-inflammatories (food, herbs, spices, nutraceuticals, botanicals)
• Gut repair (food, herbs, spices, nutraceuticals, botanicals)
• Immune enhancers (food, herbs, spices, nutraceuticals, botanicals)
• Demulcients (herbs)
interaction of various factors contributing to chronic intestinal inflammation in a genetically susceptible host
Pathogenesis of IBD

<table>
<thead>
<tr>
<th>Initiating Events</th>
<th>Mucosal Damage</th>
<th>Abnormal Immune Response</th>
<th>Chronic Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Translocation of luminal contents</td>
<td>Th1 vs. Th2</td>
<td>Luminal antigens</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td>Food antigens</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td>Bacteria</td>
</tr>
<tr>
<td>Viral</td>
<td></td>
<td></td>
<td>Bacterial products</td>
</tr>
<tr>
<td>Bacterial</td>
<td></td>
<td></td>
<td>FMLP</td>
</tr>
<tr>
<td>Parasitic</td>
<td></td>
<td></td>
<td>LPS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PGPS</td>
</tr>
</tbody>
</table>

Pathogenesis of IBD

Activated Th1 Cell

IL-2, IFNγ

IL-1, IL-6, TNF-α

Lymphokines

Macrophage

IL-12

IL-1

CD4

CD45R

Memory T Cell

ADCC

Mucosal injury

ROS

Inflammation

Lymphokines

OH·

O₂⁻
Inflammatory Bowel Disease

• Chronic inflammation, tissue injury
• Gut repair is multimodal
• Increased oxidative stress both in the gut and systemically
• Uncontrolled inflammation leads to fibrosis in Crohn’s disease and higher risk of cancer in inflammatory bowel disease (IBD)
Probiotics

- Dysbiosis – unbalanced or harmful intestinal flora
- Dysbiosis contributes to illness through changes in intestinal permeability and altered gut microbiology
- Stress, food, medical drugs, environmental toxins and climate all stimulate or inhibit different types of microorganisms
**Benefits of Probiotics in IBD: Mechanisms of Action**

<table>
<thead>
<tr>
<th>Inhibit Pathogenic Bacteria</th>
<th>Improve Epithelial Function</th>
<th>Immunoregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>SCFA’s</td>
<td>IL-10, TGF</td>
</tr>
<tr>
<td>Bacteriocidal proteins</td>
<td>Healing</td>
<td>T NF, IL-12</td>
</tr>
<tr>
<td>Epithelia binding</td>
<td>Mucus</td>
<td>slgA</td>
</tr>
<tr>
<td>Epithelial invasion</td>
<td>Barrier Integrity</td>
<td>NFkB</td>
</tr>
</tbody>
</table>
## RCTs: CROHN’S DISEASE - Recurrence

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Control</th>
<th>N</th>
<th>Duration</th>
<th>Replapse: Probiotic/Control</th>
<th>P</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli Nissle</em> 1917</td>
<td>Placebo</td>
<td>28</td>
<td>12 months</td>
<td>33%/63%</td>
<td>&lt;0.05</td>
<td>Malchow 1997</td>
</tr>
<tr>
<td>VSL#3</td>
<td>5-ASA</td>
<td>40</td>
<td>12 months</td>
<td>20%/40%</td>
<td>&lt;0.05</td>
<td>Campieri et al. 2000</td>
</tr>
<tr>
<td><em>LGG</em></td>
<td>Placebo</td>
<td>45</td>
<td>12 months</td>
<td>60%/35.3%</td>
<td>0.297</td>
<td>Prantera et al. 2002</td>
</tr>
<tr>
<td><em>S. boulardii</em> + 5-ASA</td>
<td>5-ASA alone</td>
<td>32</td>
<td>6 months</td>
<td>6.3%/37.5%</td>
<td>&lt;0.05</td>
<td>Guslandi et al. 2000</td>
</tr>
</tbody>
</table>
Remission induction and maintenance effect of probiotics on ulcerative colitis: A meta-analysis

Li-Xuan Sang, Bing Chang, Wen-Liang Zhang, Xiao-Mei Wu, Xiao-Hang Li, Min Jiang
### Level A Evidence

#### Study or subgroup

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Weight (%)</th>
<th>Risk ratio M-H, random (95% CI)</th>
<th>Risk ratio M-H, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>219</td>
<td>180</td>
<td>100</td>
<td>1.35 (0.98, 1.85)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>138</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 15.63$, df = 6 ($P = 0.02$); $I^2 = 62%$</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 1.82$ ($P = 0.07$)</td>
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<td></td>
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</table>

#### Study or subgroup

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Weight (%)</th>
<th>Risk ratio M-H, random (95% CI)</th>
<th>Risk ratio M-H, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>390</td>
<td>319</td>
<td>100</td>
<td>0.69 (0.47, 1.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>109</td>
<td>125</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2 = 0.16$; $\chi^2 = 18.50$, df = 7 ($P = 0.010$); $I^2 = 62%$</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: $Z = 1.92$ ($P = 0.05$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Probiotic Foods

Dairy-based
- Yogurt
- Cheese
- Acidophilus milk
- Kefir

Nondairy-based
- Brined olives
- Salted gherkins
- Sauerkraut
- Kim chee
- Miso
- Natto
- Tempeh
- Poi
- Tanzania Togwa

Lin, D.C. NCP 18:497, 2003
Lipski, E. IN: Integrative Gastroenterology 2011
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Fiber</th>
<th>Study</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez-Banares</td>
<td>1999</td>
<td>Plantago Ovata seed fiber 10 gm</td>
<td>Fiber +/- Mesalamine</td>
<td>= to Mesalamine</td>
</tr>
<tr>
<td>Kanauci</td>
<td>2002</td>
<td>30 gm barley</td>
<td>Mod to active UC</td>
<td>disease activity</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallert</td>
<td>2003</td>
<td>Oat bran 60 gm (20gm fiber)</td>
<td>In remission</td>
<td>abd pain Increase fecal butyrate</td>
</tr>
<tr>
<td>Welters</td>
<td>2002</td>
<td>Inulin 24 gm</td>
<td>IAPA</td>
<td>pouch inflammation</td>
</tr>
</tbody>
</table>
“Relax, sir.
The hair in your soup provides fiber.”
Short Chain Fatty Acids

Malabsorbed carbohydrate and nondigestible fibers are fermented by colonic bacteria into short chain fatty acids (SCFA).

- SCFA primary fuel for colon
- SCFA absorbed by colonic mucosa & used as energy in SBS
- SCFA enhance sodium and water absorption
- SCFA exert trophic effects in SB and colon
- Regulates cell proliferation, differentiation, carcinogenesis
- Role in immunomodulation

Jeppesen et al. JPEN 1999;23:S101-S104
Royall D et al. Am J Gastroenterol 1992;87:751
SCFA Enemas
(60-100 mmol/100ml 1-2 times/day)

Butyrate, acetate, and propionate are SCFAs, which are by-products of colonic fermentation.

- Primary fuel for the colon
- Trophic effects, increases sodium/water absorption
- Mucosal levels are decreased in distal ulcerative colitis
- SCFA enemas are used for refractory distal ulcerative colitis

Prospective Studies of SCFA for Left-sided Ulcerative Colitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. Patients (Treatment)</th>
<th>Study Duration (wk)</th>
<th>Butyrate Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheppack¹³⁷</td>
<td>Single-blind</td>
<td>10 (Butyrate enema)</td>
<td>2</td>
<td>100 mM</td>
<td>↓ Stool frequency, hematochezia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ Endoscopic, histologic score</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no change</td>
</tr>
<tr>
<td>Breuer²⁰</td>
<td>Crossover</td>
<td>10 (Placebo)</td>
<td></td>
<td>100 mL bid</td>
<td>↓ Disease activity index</td>
</tr>
<tr>
<td></td>
<td>Open-label</td>
<td>10 (SCFA⁺ enema)</td>
<td>6</td>
<td>40 mM</td>
<td>↓ Mucosal histology score</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 mL bid</td>
<td></td>
</tr>
<tr>
<td>Hillary-Steinhart⁶⁸</td>
<td>Open-label</td>
<td>10 (Butyrate enema)</td>
<td>6</td>
<td>80 mM</td>
<td>↓ Disease activity index</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60 mL qd</td>
<td>60% Response</td>
</tr>
<tr>
<td>Patz¹¹⁵</td>
<td>Open-label</td>
<td>10 (SCFA⁺ enema)</td>
<td>6</td>
<td>40 mM</td>
<td>40% Complete remission</td>
</tr>
<tr>
<td>Vernia¹⁵⁴</td>
<td>Open-label</td>
<td>9 (Butyrate + 5-ASA enema)</td>
<td>6</td>
<td>80 mM</td>
<td>5/10 Endoscopic and clinical improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 mL bid</td>
<td>7/9 Endoscopic, clinical, and histologic improvement</td>
</tr>
</tbody>
</table>

*SCFA = short-chain fatty acid—solution containing 80 mM acetate, 30 mM propionate, and 40 mM butyrate.
⁺SCFA = short-chain fatty acid—solution containing 60 mM acetate, 30 mM propionate, and 40 mM butyrate.
5-ASA = 5-aminosalicylic acid.
- Extracellular matrix formation
- Cell migration
- Differentiation
- Immune regulation
- Tissue remodeling
- Regulates inflammation
- Promotes healing
TGF-β-enriched Formulas for Crohn’s Disease Using Whey Protein

• 3 cohort studies evaluated TGF-β-enriched formula in patients with Crohn's disease
• TGF-β diet for 8 weeks as sole nutrition, improvements:
  – ESR and CRP levels
  – Serum albumin levels
  – Mucosal healing, Clinical Disease Activity
  – Serum IL-1β, IL-8, and IFN-γ
• The relapse rate was high after remission achieved with nutritional therapy

Nutritional Supplementation with Polymeric Diet Enriched with Transforming Growth Factor-Beta 2 for Children with Crohn's Disease

Corina Hartman MD1,8, Drora Berkowitz MD2,9, Batia Weiss MD3,8, Ron Shaoul MD4,9, Arie Levine MD5,8, Orly Eshach Adiv MD2,9, Riki Shapira MD1,8, Akiva Fradkin MD3, Michael Wilschanski MD6, Ada Tamir PhD7, Tel Aviv Center of Israel, Petah Tikva, Israel

Center, Tel Hashomer, Israel

Center, Jerusalem, Israel

Children

Inflammatory mediators secreted from the intestine in the intestinal inflammation and providing are essential to prevent or remedy growth lution, enteral diets – both elemental and poly- primary therapy in Crohn's disease have been disease remission without concomitant use of [3,4]. Furthermore, supplementary enteral nutri- therapy and after remission is induced may be the prolongation of remission and promotion [8]. The pathways by which enteral diets may inflammation are manifold. Practically, there is enteral diet has a direct effect on the gut cytokine production and the accompanying J. Modifications of the enteral diet composition

Figure 1. Means and SD for PCDAI scores at the start and follow-up and ΔPCDAI in the Modulen IBD, Ensure Plus and non-supplemented groups

Omega-6 & Omega-3

Omega-6 Fatty Acids (e.g., corn, safflower, sunflower oils)
- Linoleic Acid
  - delta-6-desaturase*
  - Gamma-Linolenic Acid (GLA) (e.g., evening primrose, borage, black currant seed oils)
  - Dihomo-Gamma-Linolenic Acid (DGLA)
  - PGE1 (anti-inflammatory)
  - Arachidonic Acid (cyclooxygenase, lipooxygenase)
    - PGE2 (pro-inflammatory)
    - LTB4 (pro-inflammatory)
- Proinflammatory Series 2 Prostaglandins
- Series 4 Leukotrienes

Omega-3 Fatty Acids (e.g., canola, flaxseed oil, fish oils)
- Alpha-Linolenic Acid (LNA)
  - delta-6-desaturase*
  - Steridonic Acid
  - Eicosatraenoic Acid (delta-5-desaturase)
  - EPA (anti-inflammatory) (e.g., fish oils)
    - DHA
  - Proinflammatory Series 3 Prostaglandins
  - Series 5 Leukotrienes

* Factors thought to impair delta-6-desaturase activity include Mg, Zn, and Be deficiency; aging; alcohol; trans fatty acids; and high cholesterol levels.
Omega-3, -6 Modulation of Arachidonic Acid Cascade

Omega-3 Fatty Acids
- Fish
- Walnuts
- Flax
- Canola oil

Omega-6 Fatty Acids
- Corn
- Primrose
- Safflower oil
- Red meat
### Effects of Omega-3 Fatty Acids on Factors Involved in the Pathophysiology of Inflammation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Omega-3 Fatty Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet activating factor (PAF)</td>
<td>↓</td>
</tr>
<tr>
<td>Platelet-derived growth factor (PDGF)</td>
<td>↓</td>
</tr>
<tr>
<td>Oxygen free radicals</td>
<td>↓</td>
</tr>
<tr>
<td>Lipid hydroperoxides</td>
<td>↓</td>
</tr>
<tr>
<td>IL-1, IL-6, and TNF</td>
<td>↓</td>
</tr>
<tr>
<td>NF-κB, PPARs adhesion molecules</td>
<td>↓</td>
</tr>
</tbody>
</table>
Fish Oils and IBD: Animal Studies

6/6 mice models of ulcerative colitis showed protection from injury and healing with omega-3 fatty acids.

## Fish Oils & UC
### Induction of Remission


* 72% weaned off or reduced medication dose. N=159

**Level A Evidence**

<table>
<thead>
<tr>
<th>Study</th>
<th>EPA</th>
<th>DHA</th>
<th>Clinical Remission</th>
<th>Endoscopic Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almallah 1998</td>
<td>3.2 g/d</td>
<td>2.4 g/d</td>
<td>p&lt;0.05</td>
<td>p=0.013</td>
</tr>
<tr>
<td>Aslan 1992</td>
<td>2.7 g/d</td>
<td>1.8 g/d</td>
<td>*p&lt;0.05</td>
<td>NR</td>
</tr>
<tr>
<td>Stenson 1992</td>
<td>3.24 g/d</td>
<td>2.16 g/d</td>
<td>p=0.001</td>
<td>p=0.054</td>
</tr>
</tbody>
</table>

Fish Oil for the Maintenance of Ulcerative Colitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawthorne 1992</td>
<td>8/19</td>
<td>7/15</td>
<td></td>
<td>25.43</td>
<td>0.90 [0.42, 1.92]</td>
</tr>
<tr>
<td>Loeschke 1996</td>
<td>18/31</td>
<td>18/33</td>
<td></td>
<td>56.69</td>
<td>1.06 [0.69, 1.64]</td>
</tr>
<tr>
<td>Mantzaris 1996</td>
<td>6/22</td>
<td>5/18</td>
<td></td>
<td>17.88</td>
<td>0.98 [0.36, 2.70]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>72</td>
<td>66</td>
<td></td>
<td>100.00</td>
<td>1.01 [0.71, 1.44]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 0.15, df = 2 (P = 0.93), I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)

Fish Oil for the Maintenance of CD


<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (random)</th>
<th>Weight</th>
<th>RR (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Figure 1a: 1-year relapse rate, all studies (Crohn's)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belluzzi 1996</td>
<td>11/39</td>
<td>27/39</td>
<td>11.98</td>
<td>0.41</td>
<td>0.24, 0.70</td>
</tr>
<tr>
<td>Lorenz-Meyer 1996</td>
<td>40/70</td>
<td>36/65</td>
<td>21.40</td>
<td>1.03</td>
<td>0.77, 1.39</td>
</tr>
<tr>
<td>Belluzzi 1997</td>
<td>2/26</td>
<td>5/24</td>
<td>2.19</td>
<td>0.37</td>
<td>0.08, 1.73</td>
</tr>
<tr>
<td>Romano 2005</td>
<td>11/18</td>
<td>19/20</td>
<td>17.56</td>
<td>0.64</td>
<td>0.44, 0.94</td>
</tr>
<tr>
<td>Feagans 2008: EPIC 1</td>
<td>54/183</td>
<td>62/180</td>
<td>21.24</td>
<td>0.86</td>
<td>0.63, 1.16</td>
</tr>
<tr>
<td>Feagans 2008: EPIC 2</td>
<td>84/187</td>
<td>94/188</td>
<td>25.62</td>
<td>0.90</td>
<td>0.73, 1.11</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>523</td>
<td>516</td>
<td></td>
<td>100.00</td>
<td>0.77, 0.98</td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 12.01, df = 5 (P = 0.03), I^2 = 58.4%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.16 (P = 0.03)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Figure 1b: 1-year relapse rate, enteric-coated studies** |
| Belluzzi 1996          | 11/39     | 27/39   | 15.61       | 0.41   | 0.24, 0.70  |
| Belluzzi 1997          | 2/26      | 5/24    | 2.95        | 0.37   | 0.08, 1.73  |
| Romano 2005            | 11/18     | 19/20   | 22.50       | 0.64   | 0.44, 0.94  |
| Feagans 2008: EPIC 1   | 54/183    | 62/180  | 26.91       | 0.86   | 0.63, 1.16  |
| Feagans 2008: EPIC 2   | 84/187    | 94/188  | 26.04       | 0.90   | 0.73, 1.11  |
| **Total (95% CI)**     | 453       | 451     |             | 100.00 | 0.71, 0.93  |
| Test for heterogeneity: $\chi^2 = 9.43, df = 4 (P = 0.05), I^2 = 57.6\%$ |
| Test for overall effect: $Z = 2.45 (P = 0.01)$ |

| **Figure 1c: 1-year relapse rate, excluding abstracts** |
| Belluzzi 1996          | 11/39     | 27/39   | 12.25       | 0.41   | 0.24, 0.70  |
| Lorenz-Meyer 1996     | 40/70     | 36/65   | 21.88       | 1.03   | 0.77, 1.39  |
| Romano 2005            | 11/18     | 19/20   | 17.96       | 0.64   | 0.44, 0.94  |
| Feagans 2008: EPIC 1   | 54/183    | 62/180  | 21.71       | 0.86   | 0.63, 1.16  |
| Feagans 2008: EPIC 2   | 84/187    | 94/188  | 26.19       | 0.90   | 0.73, 1.11  |
| **Total (95% CI)**     | 497       | 492     |             | 100.00 | 0.78, 1.00  |
| Test for heterogeneity: $\chi^2 = 10.93, df = 4 (P = 0.03), I^2 = 63.4\%$ |
| Test for overall effect: $Z = 2.00 (P = 0.05)$ |
Combined oral supplement to determine whether enteral nutrition can provide steroid sparing effect (n=121, 86 completed study) for 6 months

18 oz. of either:

- Nutritionally balanced oral supplement (UCNS)
- CHO-based placebo

UCNS Formula per 8 oz.

- 310 kcal [16.1/49.7/6.5% protein/CHO/lipid]
- Fish oil (1.09 g EPA/0.46 g DHA)
- 3.5 g EPA/DHA per day
- FOS 2.9 g
- Gum arabic 2.2 g
- Calcium (mg) - 432
- Phosphorus (mg) - 300
- Magnesium (mg) - 108
- β-carotene (μg) - 1185
- Vitamin A (IU) - 1320
- Vitamin D (IU) - 192
- Vitamin E (IU) - 72
- Vitamin K (μg) - 32
- Vitamin C (mg) - 156
- Folic acid (μg) - 456
- Zn (mg) - 7
- Se (μg) - 22
An Oral Supplement Enriched With Fish Oil, Soluble Fiber, and Antioxidants for Corticosteroid Sparing in Ulcerative Colitis: A Randomized, Controlled Trial

Figure 1. Plasma phospholipid concentrations of AA, EPA, and DHA in completed patients receiving either placebo (n = 50) or UCNS (n = 36) at baseline and after 3 and 6 months of study. Values are means ± SE. *P < .001 vs. placebo.

Figure 2. Plasma concentrations of α-tocopherol and β-carotene in completed patients receiving either placebo (n = 50) or UCNS (n = 36) at baseline and after 3 and 6 months of study. Values are means ± SE. *P < .001 vs. placebo.
An Oral Supplement Enriched With Fish Oil, Soluble Fiber, and Antioxidants for Corticosteroid Sparing in Ulcerative Colitis: A Randomized, Controlled Trial

Vitamin D is converted to 25(OH)D in the liver and further to 1,25(OH)₂D in the kidney. 1,25(OH)₂D is involved in the regulation of calcium and bone health, blood pressure, and immune function. Milk, orange juice, salmon, and supplements are sources of Vitamin D.

- **Regulation of Cell Growth** (cancer prevention)
- **Regulation of Immune Function** (diabetes type 1, MS, RA, autoimmune disease prevention)
- **Calcium, Muscle Bone Health & Regulation of Blood Pressure Insulin Production** (heart disease and diabetes prevention)
Change in Nutrition and Disease Measures After 4 Months of Supplementation.

After 4 months, those patients with higher EPA levels had a significantly higher IBDQ (mean ± SD, 179.1 ± 26.6 vs 114.6 ± 35.9; \( P < .001 \)) and lower CDAI (116 ± 94.5 vs 261.8 ± 86.5; \( P = .005 \)) compared with those with lower levels of EPA.

The Effects of an Oral Supplement Enriched With Fish Oil, Prebiotics, and Antioxidants on Nutrition Status in Crohn’s Disease Patients

- Increased fat-free and fat mass deposition,
- Improved vitamin D status
- Improvement in quality of life and lower disease activity
- Open label; high drop out rate; small sample

Inflammatory Bowel Disease Questionnaire (IBDQ) and Crohn’s Disease Activity Index (CDAI) during treatment with IBD Nutritional Formula (IBDNF) supplementation in patients with final eicosapentaenoic acid (EPA) >2%

There was a significant increase in IBDQ (+41.4 [23.1, 47.0]; $P = .002$) and decrease in CDAI (−47.8 [−65, −37.8]; $P = .05$) in patients with higher EPA levels

Clinical trial: vitamin D3 treatment in Crohn’s disease – a randomized double-blind placebo-controlled study

108 patients with Crohn's disease in remission, of which fourteen were excluded later. Patients were randomized to receive either 1200 IU vitamin D3 (n = 46) or placebo (n = 48) once daily during 12 months. The primary endpoint was clinical relapse.
Pathogenesis of IBD

Activated Th1 Cell
- IL-2, IFN-γ

Lymphokines
- IL-2, IFN-γ

IL-12

Ag

4F2

IL-2-R

T9

IL-1

Macrophage
- IL-1
- IL-6
- TNF-α

IL-8, MIP-1α

ADCC

Mucosal injury

ROS

Inflammation

Memory T Cell
- CD45R
- CD4

Lymphokines
- OH·
- O₂⁻

TNF-α

CD14

(±)
Impaired Cellular Defense Mechanisms in IBD

Nutritional

- Vitamin E
- Beta-Carotene
- Catalase
- Cu/Zn SOD
- Mn
- SOD + Glutathione Peroxidase + GSH
- LIPID BILAYER OF ALL CELLULAR MEMBRANES
- NUCLEUS
- LYSOSOMES
- PEROXISOMES
- CYTOPLASM
- MITOCHONDRION
- DNA
- GSH
- Glutathione Peroxidase
- Vitamin C
- Vitamins C and E
- Beta-Carotene
Pharmaceutical modulation of the Arachidonic Acid Cascade

Cell membrane

Phospholipase A2

Arachidonic Acid

Cortisone

Indomethacin

Aspirin

Ibuprofen

Sulfasalazine

Prostaglandin 2 series

Cyclooxygenase

Lipoxygenase

Thromboxane A2

Leukotrienes

SRS-A

Sulfasalazine

Sulfasalazine

Colchicine

X

X

X

X

X

X
Botanical Modulation of Arachidonic Acid Cascade

Figure 3. Botanical modulation of arachidonic acid cascade. Polyphenols have a number of different mechanisms for downregulating inflammation and modulating immunity. A number of botanicals, including polyphenols (curcumin, boswellia, quercitin and ginger), interfere with the production of noxious proinflammatory eicosanoids such as prostaglandin-2 series leukotrienes such as SRS-A and thromboxane A2 via inhibition of the enzymes COX-2 and 5'-lipooxygenase.

SRS-A: Slow reactive releasing substance.

Natural Products with Anti-inflammatory Actions

NF-κB inhibitors:
- Curcuminoids
- Ginger
- Boswellia
- Green tea extract (EGCG)
- Bromelain
- Rosemary (carnosol)

Inflammatory inhibitors (NF-κB independent):
- Caffeic acid phenyl ester (CAPE)
- Bee propolis
- Resveratrol
- 1,25-(OH)₂D₃
- GLA (evening primrose oil)
- EPA (fish oil)

- Grape seed extract
- Phytolens (lentils)
- Probiotics
- Alpha-lipoic acid
- DHA (fish oil)
- ALA (flaxseed oil)
- White willow bark
- Devil’s claw
Phytonutrients and Botanicals Likely to be Useful in Inflammatory Conditions of the GI Tract
Polyphenols

- Phytochemicals found in food and beverages that are derived from plants
- Nonessential
- Anti-inflammatory and vasculoprotective properties
- Four polyphenols with anti-inflammatory properties have been studied in human and animal models of colitis:
  - Curcumin (turmeric)
  - Resveratrol (grapes, wine)
  - EGCG (green tea)
  - Quercetin (apples, onions, leafy veggies, tea)
Polyphenols Attenuate Inflammation and Injury
### Prophylactic and Therapeutic Effects of Polyphenols for Colitis

<table>
<thead>
<tr>
<th>Polyphenol</th>
<th>N</th>
<th>Route, dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resveratrol</td>
<td>2</td>
<td>5-10 mg/kg, 2/2 IG</td>
<td>2/2 improvement: clinical, path, mediators, cytokines</td>
</tr>
<tr>
<td>EGCG</td>
<td>3</td>
<td>5 g/L, 50 mg/kg/D, 1 IP, 2 PO</td>
<td>3/3 improvement: clinical, path, mediators, cytokines</td>
</tr>
<tr>
<td>Curcumin</td>
<td>6</td>
<td>2%, 30-300 mg/kg/D, 6 PO, 1 IP</td>
<td>6/6, improvement: clinical, path, mediators, cytokines, markers 4/7 ↑ survival</td>
</tr>
<tr>
<td>Quercetin</td>
<td>6</td>
<td>5 PO/IG, 0.25-50 mg/kg/D, enema 10-100 mM/D</td>
<td>Overall 3/6 showed efficacy Enema ineffective</td>
</tr>
</tbody>
</table>

**Animal Studies**
Please Pass the Berries!

<table>
<thead>
<tr>
<th>Food</th>
<th>Duration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra virgin olive oil</td>
<td>Single meal</td>
<td>↓ TXB2 and LTB4</td>
</tr>
<tr>
<td>Tomato juice</td>
<td>10 days</td>
<td>↓ neutrophil airway influx in asthmatics</td>
</tr>
<tr>
<td>Tomato drink</td>
<td>26 days</td>
<td>↓ TNFalpha production by whole blood</td>
</tr>
<tr>
<td>Whole tomatoes</td>
<td>28 days</td>
<td>No change in CRP</td>
</tr>
<tr>
<td>Walnuts</td>
<td>Single meal</td>
<td>↓ monocyte mRNA for TNFα &amp; IL-6</td>
</tr>
<tr>
<td>Red wine</td>
<td>4 weeks</td>
<td>Reduced CRP and fibrinogen</td>
</tr>
<tr>
<td>Garlic powder</td>
<td>3 months</td>
<td>No effect on CRP, TNF-α</td>
</tr>
<tr>
<td>Flaxseed flour</td>
<td>2 weeks</td>
<td>↓ CRP, fibronectin &amp; serum amyloid A in obese subjects</td>
</tr>
<tr>
<td>Tea, black</td>
<td>12 weeks</td>
<td>40-50% ↓ CRP in subjects w/CRP &gt; 3mg/L.</td>
</tr>
<tr>
<td>Tea, black</td>
<td>6 weeks</td>
<td>↓ CRP &amp; platelet aggregation in healthy men</td>
</tr>
<tr>
<td>Tea, green</td>
<td>4 weeks</td>
<td>No effect on CRP in men; no significant effect on CRP in male smokers</td>
</tr>
<tr>
<td>Cherries, sweet</td>
<td>4 weeks</td>
<td>↓ CRP and CCL5, no effect on IL-6 in healthy adults</td>
</tr>
</tbody>
</table>
Red Wine Cools Colonic Inflammation in UC

Fig. 1. Median stool calprotectin before and after moderate red wine consumption.

Fig. 2. Increased permeability by urinary L/M ratio after moderate wine consumption.

Digestion 2011 Aug 26;84(3):238-244.
Turmeric (*Curcuma longa*)

Mechanism of action:
- Inhibits TNF-α
- Dual inhibitor of arachidonic acid metabolism
- Cortisone-like inhibitory action on phospholipases
- Antioxidant activity

Note: Turmeric is a potent inhibitor of transcription factor NF-κB
Turmeric (*Curcuma longa*): Maintenance Therapy for Ulcerative Colitis

- Randomized, multicenter, double-blind, placebo-controlled trial from Japan
- 97 patients enrolled, 89 completed study
- All took mesalamine/sulfasalazine
- Curcumin 1 g BID vs. placebo
- Clinical and endoscopic activity index (CAI, EI) end points:
  - Recurrence @ 6 mo (on drug), 12 mo (off)
  - CAI, EI

Curcumin in Ulcerative Colitis

Figure 2. The Kaplan-Meier curves showing the efficacy outcomes during the 6 months of therapy and 6 months of follow-up.

## Boswellia and IBD

<table>
<thead>
<tr>
<th>Author</th>
<th>Design/#</th>
<th>Disease</th>
<th>Control</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madish et al</td>
<td>DBRCT (31)</td>
<td>Collagenous colitis</td>
<td>Placebo</td>
<td>6 wks</td>
<td>Maintenance of remission superior with Boswellia</td>
</tr>
<tr>
<td>Gupta et al</td>
<td>Randomized (30)</td>
<td>IBD</td>
<td>Sulfasalazine</td>
<td>6 wks</td>
<td>Induction of remission superior with Boswellia</td>
</tr>
<tr>
<td>Gupta et al</td>
<td>Randomized (30)</td>
<td>UC</td>
<td>Sulfasalazine</td>
<td>6 wks</td>
<td>Induction of remission not different</td>
</tr>
</tbody>
</table>
Nutritionals Showing Efficacy in IBD

Solid Evidence
- Elemental Diet
- Modulen
- Prebiotics
- Probiotics
- Turmeric
- Boswellia
- Fish Oils

Single Studies
- Lycopene
- Aloe vera
- Ginger
- Wheatgrass juice
- UCNS
- CDNS
### Therapeutic Modalities for IBD

<table>
<thead>
<tr>
<th>Modality</th>
<th>Level of Evidence</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3 fatty acids</td>
<td>B</td>
<td>Low</td>
</tr>
<tr>
<td>Modulen (TGF-b)*</td>
<td>B</td>
<td>na</td>
</tr>
<tr>
<td>Curcumin</td>
<td>B</td>
<td>na</td>
</tr>
<tr>
<td>Probiotics</td>
<td>A</td>
<td>low</td>
</tr>
<tr>
<td>Butyrate enemas</td>
<td>B</td>
<td>na</td>
</tr>
<tr>
<td>Diet</td>
<td>B</td>
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<tr>
<td>Azathiopurine</td>
<td>B</td>
<td>high</td>
</tr>
<tr>
<td>Aminosalicylates</td>
<td>A</td>
<td>moderate</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>A</td>
<td>high</td>
</tr>
</tbody>
</table>

* Transforming growth factor
Nutritional Modulation of IBD
Take Home Sticky Points

• Polyphenols, fish oils, probiotics, vitamin D, antioxidants: down regulate inflammation to “cool the fire in the gut”

• Short chain fatty acids are colonic –specific anti-inflammatory nutrients

• High ORAC foods, wild cold-water fish, etc. Think of food as medicine first!
“Let medicine be thy food and let food be thy medicine”

Hippocrates