Prebiotics, Probiotics, Synbiotics & Antibiotics for IBS

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University of Michigan

The Gut Microbiome in Health and GI Disease

- Bacteria exceed the number of host somatic cells by > one order of magnitude
  - Gut bacterial population ~100 trillion
  - 500-1000 different species of bacteria
  - 60% of fecal biomass is from bacteria
- Microbiome exerts important effects on:
  - Structure, physiology, biochemistry, immunology, maturation of vasculature, and gene expression
  - Bidirectional effects on gut neuromotor function
  - Role in IBD, SIBO, IBS, diverticular disease?
  - Differences in microflora reported in IBS vs. healthy controls

Barbara et al. Am J Gastroenterol 2005;100:2580
Intrinsic and extrinsic factors affecting gut microbiota distribution and composition

Integrated conceptual framework of the pathophysiology of IBS.
Dysbiosis and IBS

- Dysbiosis
  - Genetic Susceptibility
  - Environmental Factors

  Altered Permeability
  Increased Antigen Presentation
  Mast Cell Activation

ExtraGI Symptoms
Systemic Cytokines & Chemokines

IBS
Altered Enteric Neuronal & Smooth Muscle Function

Key Components of Bidirectional Interactions between Brain and Gut

Mayer EA. Gastroenterology 2014;146:1500.
The Gut Microbiota: A Potential IBS Treatment Target

- Probiotics?
- Prebiotics?
- Synbiotics?
- Antibiotics?
- Functional Medical Foods?
- Diet?
- FMT?
Possible Mechanisms of Probiotic Activity

Interfere with growth or survival of bacteria in gut lumen
Effects on bile acids
Effects on barrier function, mucosal immune system & enterendocrine cells

Affect systemic immune system

Adapted from Rijkers GT, et al. J Nutr. 2010;140:671S-676S

Examples of Probiotic Products

**Single-organism Probiotics**

- E coli Nissle 1917
- L salivarius UCC4331
- L rhamnosus GG
- L casei
- L plantarum 299v
- L reuteri
- L casei
- L rhamnosus GG
- B infantis 35624
- B animalis DN-173010
- Saccharomyces boulardii

**Combination Probiotics**

- VSL #3 (bifidobacteria, lactobacilli, Streptococcus salivarius thermophilus)
- Lacteol Fort (L acidophilus LB, lactose monohydrate, calcium carbonate, silicic acid, talc, magnesium stearate, anhydrous lactose)

Regulated as supplements in the US
Utility of Probiotics for IBS: A Statistical Review and Meta-analysis

- Forty-three RCTs included
- RR of IBS symptoms persisting with probiotics vs placebo was 0.79 (95% CI 0.70-0.89)
  - Probiotics had beneficial effects on global IBS, abdominal pain, bloating and flatulence scores
  - Effects of individual species or combinations marginal to non-existent
- NNT = 7 (95% CI 4-12.5)
- NNH - 35


Bifidobacter infantis 35624 for IBS

Abdominal Pain/Discomfort

Whorwell, Am J Gastroenterol 2006; 101:1581

* Likert scale=0 (none) to 5 (severe); treatment was stopped at 4 weeks.
**Proportion Reporting Adequate Relief of IBS symptoms**

- **B. lactis CNCMI-2494 (1.25×10^10 cfu), S. thermophilus & L. bulgaricus (1.2×10^9 cfu)**

  - N=88/60
  - N=91/49

  *P = .027

  *P = .004

  Roberts et al. BMC Gastroenterology 2013, 13:45

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**Proportion Reporting Adequate Relief of IBS symptoms**

- **L. paracasei F19, L. acidophilus La5 & Bif Bb12 in doses of 3×10^9 to 7×10^9**

  - 4 capsules qd

  No significant differences at 6 months

  Begtrup et al. Scand J Gastro 2013, 48:1127
FODMAP Microbiome Biomarkers and Response to the Low-FODMAP Diet

- 33 children with IBS completed the study
- Less abdominal pain occurred during the low FODMAP diet vs. typical US childhood diet
- Responders were enriched at baseline in taxa with known greater saccharolytic metabolic capacity
  - e.g. Bacteroides, Ruminococcaceae, Faecalibacterium prausnitzii
- Responders also enriched at baseline for 3 Kyoto Encyclopedia of Genes and Genomes orthologues
  - two relate to carbohydrate metabolism


Prebiotics and their potential role in IBS

- **Prebiotics**: Poorly absorbed selectively fermented short-chain carbohydrates which allow targeted changes in GI microbiota which confer a health benefit
  - Bran, lactulose, sorbitol are examples
  - FOS & galacto-oligosaccharides increase concentrations of luminal and mucosal *Bifidobacteria*
  - No high quality RCTs

Parkes et al. Am J Gastroenterol 2008;103:1557
Moving Beyond Elimination: Functional Foods

- “A foodstuff that provides a health benefit beyond basic nutrition, demonstrating specific health or medical benefits, including the prevention and treatment of disease” (Food & Agricultural Organization, United Nations)

- Can be categorized as:
  - Conventional foods that contain bioactive components
  - Foods enriched or fortified with bioactive food compounds
  - Synthesized food ingredients such as indigestible oligosaccharides that provide a health benefit, or serve as precursors to compounds that provide a health benefit

Crowe KM, J Acad Nutr Diet 2013;113:1096
http://www.fao.org/docrep/004/y2775e/y2775e08.htm

Production of short chain organic acids – a major ecosystem service from the microbiome

- Butyric acid (butyrate)
  - preferred energy source for colonocytes
  - maintains integrity of gut mucosa
  - regulates satiety
  - modulates cancer risk regulates colonocyte cell cycles

(Tremaroli & Backhed 2012 Nature; Lee & Hase 2014 Nature Chemical Biology)
Resistant Starch increases butyrate in Healthy Volunteers

Dynamics of both starch-degrading and butyrogenic bacteria explain much of the observed variation

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- **Synbiotics**: preparations containing both a prebiotic and probiotic in order to improve GI probiotic colonization

*Parkes et al. Am J Gastroenterol 2008;103:1557
Neish. Gastroenterol 2009;136:65*
Prebiotics, Synbiotics and Postbiotics for IBS

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- **Synbiotics**: preparations containing both a prebiotic and probiotic in order to improve GI probiotic colonization
- **Postbiotics**: isolated bacterial components which are administered as therapeutics

Parkes et al. Am J Gastroenterol 2008;103:1557

The Gut Microbiota: A Potential IBS Treatment Target

Rifaximin vs. Placebo for Non-C IBS: Daily AR of IBS Symptoms from Weeks 1-12

Rifaximin for Global Improvement in IBS:
A meta-analysis

<table>
<thead>
<tr>
<th>Measure Outcomes</th>
<th>Response rates (%)</th>
<th>Weight</th>
<th>ARR</th>
<th>NNT</th>
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</thead>
<tbody>
<tr>
<td>Sharara</td>
<td>27.0 9</td>
<td>1.4%</td>
<td>18%</td>
<td>5.6</td>
</tr>
<tr>
<td>Pimental</td>
<td>32.5 9</td>
<td>1.6%</td>
<td>23.5%</td>
<td>4.3</td>
</tr>
<tr>
<td>Lembo</td>
<td>52.3 44.2</td>
<td>25.2%</td>
<td>8.1%</td>
<td>12.3</td>
</tr>
<tr>
<td>Target 1</td>
<td>40.8 31.2</td>
<td>34.9%</td>
<td>9.6</td>
<td>10.4</td>
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<tr>
<td>Target 2</td>
<td>40.6 32.2</td>
<td>36.8%</td>
<td>8.4</td>
<td>11.9</td>
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<tr>
<td>Overall</td>
<td>43.3 34.2</td>
<td>100%</td>
<td>9.1</td>
<td>11.0</td>
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</table>

Heterogeneity: $\chi^2=5.26, df=4, I^2=24\%, p=0.26$

Menees et al. AJG 2012;107:28
Rifaximin for IBS: Bloating

<table>
<thead>
<tr>
<th>Measure Outcomes</th>
<th>Response rates (%)</th>
<th>Weight ARR NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rifaximin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Pimental</td>
<td>41.8</td>
<td>15.9</td>
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<tr>
<td>Lembo</td>
<td>46.1</td>
<td>39.6</td>
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<td>28.7</td>
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<tr>
<td>Target 2</td>
<td>41.0</td>
<td>31.9</td>
</tr>
<tr>
<td>Overall</td>
<td>41.8</td>
<td>32.4</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 3.94, df=3, P=24\%$

Menees et al. AJG 2012;107:28

Pooled Safety Analysis of Rifaximin for Non-C IBS

- Data analyzed from 2 phase 3 and 1 phase 2b trials of rifaximin

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin (n=1103)</th>
<th>Placebo (n=829)</th>
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<tbody>
<tr>
<td>Any TEAE</td>
<td>52.5%</td>
<td>52.6%</td>
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<tr>
<td>Serious TEAE</td>
<td>1.5%</td>
<td>2.2%</td>
</tr>
<tr>
<td>TEAE resulting in discontinuation</td>
<td>2.0%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Any GI TEAE</td>
<td>12.2%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.1%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.4%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.4%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Any Infection TEAE</td>
<td>8.5%</td>
<td>9.5%</td>
</tr>
<tr>
<td>C. difficile colitis</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Schoenfeld, et al. APT 2014;39:1161
TARGET 3 – IBS-D Responder Enriched
Rifaximin Retreatment Trial

TARGET 3
n = 2679

Discontinued
Early
n = 248

Non-Responder
n = 1257 (54%)

Responder
n = 1074 (46%)

n = 2331

No Relapse
n = 382 (36%)

Experienced Relapse
n = 692 (64%)*

1st Repeat Treatment

Placebo
n = 308

Rifaximin
n = 328

2nd Repeat Treatment

Placebo
n = 283

Rifaximin
n = 295

Abdominal Pain and Stool Consistency at
First and Second Repeat Treatment

LOCF Analysis

Responder: Subject responding to IBS-related Abdominal Pain and Stool Consistency for ≥2 of 4 weeks

p = 0.0051

Δ = 9.8

35.4

25.6

First Repeat Treatment

Rifaximin

Placebo

p = 0.0375

Δ = 7.6

36.9

29.3

Second Repeat Treatment

Rifaximin

Placebo

*56 (5%) not randomized due to enrollment closure
William D. Chey, MD, FACG

**Improvement in IBS-D Symptoms During First and Second Double-Blind Repeat Treatment Phases**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>1st Repeat Treatment</th>
<th>2nd Repeat Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RFX (n=328) PBO (n=308)</td>
<td>p-value</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>53.0% 43.8%</td>
<td>0.0212</td>
</tr>
<tr>
<td>Stool Consistency</td>
<td>45.1% 37.0%</td>
<td>0.0241</td>
</tr>
<tr>
<td>Urgency</td>
<td>48.5% 39.6%</td>
<td>0.0251</td>
</tr>
<tr>
<td>Bloating</td>
<td>50.3% 42.2%</td>
<td>0.0345</td>
</tr>
</tbody>
</table>

Chey et al DDW 2015

**Antibiotics for IBS: Points to Consider**

- Reasons for symptom improvement unclear
  - SIBO vs. alteration of colonic flora/fermentation?
- Optimal diagnostic test for SIBO unclear
  - Breath test results may not predict response to antibiotics
- Optimal antibiotic therapy unclear
- Benefits appear transient
  - How can we increase the durability of response?
- Potential consequences of repeated, widespread antibiotic use?

Chey. AGA Perspectives 2009;4:5-8
IBS Treatments Aimed at the Gut Microbiota: Summary

- Agents that influence the gut microbiota offer a potential target in patients with IBS
- Specific probiotics may improve IBS symptoms in a subset of patients
- Prebiotics remain to be adequately tested in clinical trials
- Antibiotics offer short term benefits to a subset of IBS sufferers
- Important questions remain regarding which patients are most likely to benefit from these strategies and whether they are safe if used over extended periods of time
- Biomarker based strategies may maximize benefits