Modulation of gut microbiota: a helping hand for IBS patients?  
*D. Waitzberg (BR)*
Modulation of Gut Microbiota: a helping hand for IBS patients

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Disclosure

• Danone speaker
• Biogaia/Ache speaker
Summary

• Gut Homeostasis, Microbiota, Brain-Gut Axis
• Irritable Bowel Syndrome
  – Definition
  – Epidemiology/ pathophysiology
  – Clinical features / Diagnosis
  – Classic Therapeutics
• Gut Microbiota in IBS
• Probiotics in IBS
• Conclusion
Intestinal Interactions in Health

Human Host

Diet and Food

Non-Digested Food Components

Digestion & Uptake Food Components

Endogenous Substrates - Mucus

Transformation of Food Components
Production of Short Chain Fatty Acids

Cellular Binding & Specific Response

Intestinal Microbiota

Diversity & Activity

Gastrointestinal Function & Health
Healthy microflora establish a well-balanced symbiotic state with the host by:

- Forming a crucial barrier against pathogens
- Development and maturation of the immune system.
- Role in the metabolism of non-digestible compounds
- Supply of essential vitamins and short chain fatty acids.

Hong SN et al. Irritable bowel syndrome and intestinal microbiota. 2014
All gut function (motor, sensory, and secretory) are controlled by intrinsic and extrinsic neural systems.
Brain – Gut - Axis

All gut function (motor, sensory, and secretory) are controlled by intrinsic and extrinsic neural systems.

These systems interact in a bi-directional network between the brain and gut => brain-gut axis.
Brain Gut Microbial Axis: A Birectional Communication

Key Components

Mayer et al. Gastroenterology. 2014 July

interstitial cells of Cajal
smooth muscle cells;
enterochromaffin
cells;

Transient modulation (e.g. in response to transient perturbations) feedback results in transient functional brain changes.

Longlasting modulation (in response to chronically altered brain output) are associated with neuroplastic brain changes.

The Gut- Microbioma Interface

Mayer et al. Gastroenterology. 2014 July
Brain Gut Microbial Axis: A Birectional Communication

Key Components

Mayer et al. *Gastroenterology*. 2014 July

**Transient modulation**
In response to transient perturbations, feedback results in transient functional brain changes.

**Long lasting modulation**
Chronically altered brain output perturbations are associated with neuroplastic brain changes.
Dysbiosis and Diseases

NAFLD
- Choline
- \(\uparrow\) Gammaproteobacteria
- \(\downarrow\) Erysipelotrichia

Type 2 diabetes
- High fat/sugar
- \(\downarrow\) Bifidobacteria

Obesity
- High carbohydrates, fat
- Low protein
- Resistance starch
- Dietary fibre
- \(\downarrow\) Bacteroidetes:Firmicutes

Atherosclerosis
- Cholesterol
- Phosphatidylcholine
- \(\downarrow\) Bacteroides
- \(\uparrow\) Ruminococcus

CRC
- Westernized diet
- Dietary fibre
- \(\downarrow\) Bacteroides

IBS
- Short-chain poorly absorbed carbohydrates
- \(\downarrow\) Bifidobacteria

IBD
- Animal milk fat
- Omega-6 PUFA
- \(\uparrow\) Enterobacteriaceae
- \(\downarrow\) F. prausnitzii
IBS Epidemiology

5-20% of the populations of Western countries

IBS affects QoL and causes substantial economic costs due to the need for medical consultation and absenteeism in the workplace

Halland M, Talley NJ. Nat Rev Gastroenterol Hepatol. 2013 Jan
What is Irritable Bowel Syndrome?

is an essential member of the functional gastrointestinal disorder (FGID) family

Rome III definition:

characterized by chronic and recurrent abdominal pain/ discomfort associated with disturbed defecation

Longstreth GF, et.al. *Gastroenterology*, 2006
Chang JY, et.al. *Curr Opin Gastroenterol* 2011
Recurrence abdominal pain or discomfort (bloating) at least 3 days/month in the last 3 months associated with 2 or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool
Diagnostic of IBS

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

Recurrent abdominal pain or discomfort (bloating) at last 3 days/month in the last 3 months associated with 2 or more of the following:
## Irritable Bowel Syndrome: Subtypes

Wall GC, et.al. World J Gastroenterol. 2014

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Definition (symptoms classified using Bristol stool form scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IBS with constipation</strong> (IBS-C)</td>
<td>&gt; 25% of stools are hard or lumpy and &lt; 25% of stools are loose/mushy or watery</td>
</tr>
<tr>
<td><strong>IBS with diarrhea</strong> (IBS-D)</td>
<td>&gt; 25% of stools are loose/mushy or watery stools and &lt; 25% are hard or lumpy</td>
</tr>
<tr>
<td><strong>Mixed IBS</strong> (IBS-M)</td>
<td>&gt; 25% of stools are loose/mushy or watery stools and &gt; 25% and hard or lumpy</td>
</tr>
<tr>
<td><strong>Unsubtyped IBS</strong></td>
<td>insufficient abnormality of stool consistency to meet criteria for IBS-C, D, or M (in the absence of antidiarrheals or laxatives)</td>
</tr>
</tbody>
</table>
IBS is a Multifactorial Disorder

IBS patients have multiple comorbidities such as dyspepsia, gastro-esophageal reflux disease, interstitial cystitis, fibromyalgia, chronic fatigue, insomnia, headache/migraine and psychiatric disturbances.
Biopsychosocial Dysfunction in IBS


Environment

Social: Family background, beliefs, learning, culture, support, imitation, illness behaviors

IBS manifestations, behaviors and outcomes
Biopsychosocial Dysfunction in IBS

Biopsychosocial Model of Dysfunction in IBS characterized by bi-directional causality and feedback

Biopsychosocial Model of Dysfunction in IBS characterized by bidirectional causality and feedback


Environment

Gut microbiota

IBS manifestations, behaviors and outcomes

The composition of the microbiota in patients with IBS is different from that of normal subjects (level 3 b evidence, grade B recommendation).

Alterations in the composition of the microbiota - dysbiosis- occur in both adult and pediatric patients with IBS (level 3 b evidence, grade B recommendation).

Due to the heterogeneity of IBS and the use of different methods for studying the gut microbiota, it is not possible to establish a microbial composition characteristic of IBS (level 3 b evidence, grade B recommendation)

Schmulson et al. Rev Gastroenterologa Mexico, 2013
The hypersensitivity to colonic distension of IBS patients can be transferred to rats through their fecal microbiota.

Sensitivity to colonic distension of IBS patients can be transferred to rats by the fecal microbiota.

The altered IBS microbiota may have important role in the hypersensitivity characterizing IBS patients through specific bacterial metabolites.
Intestinal microbiota of IBS patients (62) differed from controls (46) \((P = .0005)\)

Intestinal microbiota in IBS patients

Summary of studies

Lee KN, Lee OY. World J Gastroenterol. 2014 Jul

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Subject (n)</th>
<th>Method</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si et al</td>
<td>IBS (25)</td>
<td>Culture</td>
<td>↓ Bifidobacterium</td>
</tr>
<tr>
<td></td>
<td>Control (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malinen et</td>
<td>IBS (27)</td>
<td>qPCR</td>
<td>↑ Enterobacteriaceae</td>
</tr>
<tr>
<td></td>
<td>Control (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mattö et al</td>
<td>IBS (26)</td>
<td>Culture</td>
<td>↓ Lactobacillus in IBS-D</td>
</tr>
<tr>
<td></td>
<td>Control (26)</td>
<td>PCR-DGGE</td>
<td></td>
</tr>
<tr>
<td>Codling et</td>
<td>IBS (41)</td>
<td>PCR-DGGE</td>
<td>↓ Veillonella in IBS-C</td>
</tr>
<tr>
<td></td>
<td>Control (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ponnusamy et</td>
<td>IBS (11)</td>
<td>DGGE</td>
<td>↑ Veillonella in IBS-C</td>
</tr>
<tr>
<td></td>
<td>Control (8)</td>
<td>qPCR-16sRNA</td>
<td></td>
</tr>
<tr>
<td>Tana et al</td>
<td>IBS (26)</td>
<td>Culture</td>
<td>↓ Lactobacillus in IBS-D</td>
</tr>
<tr>
<td></td>
<td>Control (26)</td>
<td>q-PCR</td>
<td></td>
</tr>
<tr>
<td>Lyra et al</td>
<td>IBS (20)</td>
<td>qPCR</td>
<td>↓ Lactobacillus in IBS-D</td>
</tr>
<tr>
<td></td>
<td>Control (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krogius-Kurikka et al</td>
<td>IBS (10)</td>
<td>16S rRNA</td>
<td>↓ Actinobacteria and Bacteroidetes</td>
</tr>
<tr>
<td></td>
<td>Control (23)</td>
<td>sequencing</td>
<td></td>
</tr>
<tr>
<td>Kerckhoffs et al</td>
<td>IBS (41)</td>
<td>FISH</td>
<td>↓ Clostridium cocoides</td>
</tr>
<tr>
<td></td>
<td>Control (23)</td>
<td>qPCR</td>
<td></td>
</tr>
<tr>
<td>Kassinen et</td>
<td>IBS (24)</td>
<td>16S rRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control (23)</td>
<td>sequencing</td>
<td></td>
</tr>
<tr>
<td>Maukonen et</td>
<td>IBS (24)</td>
<td>PCR-DGGE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jeffery et</td>
<td>IBS (37)</td>
<td>16S rRNA</td>
<td>↑ ratio Firmicutes vs Bacteroidetes</td>
</tr>
<tr>
<td></td>
<td>Control (20)</td>
<td>pyrosequencing</td>
<td></td>
</tr>
</tbody>
</table>

DGGE: Denaturing gradient gel electrophoresis; FISH: Fluorescent in situ hybridization; IBS: Irritable bowel syndrome; qPCR: Quantitative polymerase chain reaction.
Post-Infection IBS

GI infections with pathogens:
• isolated (bacterial, viral),
• mixed (> 1 bacteria, bacteria and a virus),
• Unspecified (travelers’ diarrhoea)

have all been associated with the development of PI-IBS.
### Gut Pathogens In Development Of Post-infection IBS

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>PI-IBS % (Number infected)</th>
<th>Time-point for PI-IBS prevalence (months)</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Campylobacter</em></td>
<td>9 (188)</td>
<td>6</td>
<td>Community</td>
</tr>
<tr>
<td></td>
<td>13 (747)</td>
<td>3</td>
<td>Community</td>
</tr>
<tr>
<td><em>Shigella sonnei</em></td>
<td>8 (295)</td>
<td>12-24</td>
<td>Community</td>
</tr>
<tr>
<td></td>
<td>20 (101)</td>
<td>3</td>
<td>Community</td>
</tr>
<tr>
<td><em>Salmonella enteric</em></td>
<td>31 (38)</td>
<td>12</td>
<td>Community</td>
</tr>
<tr>
<td></td>
<td>10 (677)</td>
<td>6</td>
<td>Community</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>12 (41)</td>
<td>6</td>
<td>Community</td>
</tr>
<tr>
<td></td>
<td>4 (23)</td>
<td>3</td>
<td>Community</td>
</tr>
<tr>
<td>Mixed: &gt;1 bacteria /virus</td>
<td>27 (75)</td>
<td>6</td>
<td>Inpatient</td>
</tr>
<tr>
<td></td>
<td>7 (390)</td>
<td>6</td>
<td>Community</td>
</tr>
<tr>
<td></td>
<td>7 (192)</td>
<td>72</td>
<td>Community</td>
</tr>
<tr>
<td></td>
<td>36 (742)</td>
<td>24</td>
<td>Community</td>
</tr>
<tr>
<td></td>
<td>19 (742)</td>
<td>96</td>
<td>Community</td>
</tr>
<tr>
<td></td>
<td>32 (44)</td>
<td>6</td>
<td>Inpatient</td>
</tr>
<tr>
<td>Parasitic</td>
<td>4 (189)</td>
<td>12-120</td>
<td>Community</td>
</tr>
<tr>
<td></td>
<td>4 (318)</td>
<td>12</td>
<td>Community</td>
</tr>
<tr>
<td>Norovirus</td>
<td>4-36%</td>
<td>Time-point 6 m</td>
<td></td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pathophysiologic Role of the Microbiota in IBS

- Altered microbiota-gut-brain axis
- Altered composition and metabolic activity of the microbiota
  - Activation of mucosal immunity and inflammation
  - Increased mucosal permeability and epithelial barrier dysfunction
  - Sensory-motor disturbances
- Irritable bowel syndrome
"I'm afraid that your irritable bowel syndrome has progressed. You now have furious and vindictive bowel syndrome."
Treatment Algorithm for IBS

Assess/treat concomitant psychiatric or other disorders

Assess and perform patient education

Assess/treat celiac disease or small bowel bacterial overgrowth if indicated

Determine predominant symptoms

Consider probiotics in combination with conventional therapies for all IBS subtypes

Use at doses suggested by manufacturer for at least 4 wk

Wall GC, et.al. World J Gastroenterol. 2014
**Constipation (IBS-C)**

**First line:** slowly titrate dietary fiber up to 20 g/d and consider polyethylene glycol

**Second line:** consider addition of an SSRI

**Third line:** trial of lubiprostone or linaclotide

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**Diarrhea (IBS-D)**

**First line:** loperamide as needed or scheduled for persistent symptoms

**Second line:** consider addition of a TCA

**Third line:** hydrogen/lactose breath testing; two week course of rifaxamin

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**Abdominal pain with mixed bowel symptoms (IBS-M)**

**First line:** dicyclomine, pinavarium, trimebutine, or peppermint oil capsules for 4-6 wk

**Second line:** D/C antispasmodic if no benefit noted. Add TCA or SSRI for 4-6 wk

**Third line:** rifaxamin if residual pain/bloating

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Referral to IBS specialist if standard measures fail
New Treatments for IBS

Halland M, Talley NJ. Nat Rev Gastroenterol Hepatol. 2013 Jan

SSRI: selective serotonin reuptake inhibitor;
TCA: tricyclic antidepressant;

Probiotics
Probiotics are live microorganisms that have been considered to enhance health when administered in adequate amounts to the host.

Lee BJ, Bak YT. J Neurogastroenterol Motil. 2011
Probiotics in IBS
Potential Places to Act

• Altered Intestinal Luminal Environment
• Intestinal Mucosal Barrier Function
• Modulation of Immunity
• Neurosensory Enteric Nervous System

Lee BJ, Bak YT. J Neurogastroenterol Motil. 2011
Effect of Probiotics in IBS

- Faecal microbiota mass $\uparrow$
  $\downarrow$ constipation benefit

- Reduction of bacterial overgrowth in the small intestine
  $\downarrow$ bloating

- Normalisation of inbalanced cytokine ratio: $(\text{IL}_{10} : \text{IL}_{12})$
  $\downarrow$ inflammation

- Activation of specific opioid and cannabinoid receptors in the gut
  $\downarrow$ pain

Barret et al, World J Gastro 2008
O'Mahony et al, Gastroenterology 2005
Rousseaux et al, Nat. Med 2007

Cortesy of Remy Meyer
Beneficial Effects of Probiotics in IBS

↓ DIGESTIVE SYMPTOMS (eg BLOATING, FLATULENCE)

↓ GASTROINTESTINAL DISCOMFORT

↓ ABDOMINAL DISTENTION

SURVIVAL IN GI TRACT

MODIFICATIONS GUT PERMEABILITY

MODIFICATION GUT MICROBIOTA

GUT MOTILITY

BRAIN ACTIVITIES

GASTROINTESTINAL DISCOMFORT
Probiotics Impact in IBS

Systematic reviews

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Selection criteria</th>
<th>n of identified studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McFarland et al[73] 2008</td>
<td>RCTs in humans published as full articles or meeting abstracts in peer-reviewed journals</td>
<td>20 RCTs</td>
<td>Global IBS symptoms RR=0.77 Abdominal pain RR= 0.78</td>
</tr>
<tr>
<td>Brenner et al[79] 2009</td>
<td>RCTs; adults with IBS defined by Manning or Rome II criteria; single or combination probiotic vs placebo; improvement in IBS symptoms and/or decrease in frequency of adverse events reported</td>
<td>16 RCTs → 11 studies showed suboptimal study design</td>
<td>B.infantis Efficacy for IBS symptoms</td>
</tr>
<tr>
<td>Hoveyda et al[74] 2009</td>
<td>RCTs compared the effects of any probiotic therapy with placebo in patients with IBS</td>
<td>14 RCTs → 7 RCTs providing outcomes as dichotomous variable and 6 RCTs providing outcomes as continuous variable</td>
<td>Probiotics Efficacy for IBS symptoms, Species and strain are uncertain</td>
</tr>
<tr>
<td>Moayyedi et al[77] 2010</td>
<td>RCTs comparing the effect of probiotics with placebo or no treatment in adult patients with IBS (over the age of 16 yr)</td>
<td>19 RCTs → 10 RCTs providing outcomes as a dichotomous variable</td>
<td>Pain: B.breve, B.longum ou L.acipophilus</td>
</tr>
<tr>
<td>Ortiz-Lucas et al[77] 2013</td>
<td>RCTs comparing probiotics with placebo in treating IBS symptoms</td>
<td>24 RCTs → 11 RCTs providing outcomes as a continuous variable</td>
<td>Distension: B.breve, B.infantis or L.caei or L.plantarum</td>
</tr>
</tbody>
</table>

HKong SN et al. Irritable bowel syndrome and intestinal microbiota

March 14, 2014

Flatulence: B.breve, B.infantis L.caei, L.plantarum, B.longum, L.acidophilus, L.bulgaricus
Main Probiotics Used in IBS

• **Bifidobacterium**
• **Lactobacillus species**
• **E. coli DSM 17252**
Meta-analyses of Probiotics in IBS

<table>
<thead>
<tr>
<th>Author</th>
<th>Outcome</th>
<th>n</th>
<th>Outcome</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ortiz-Lucas 2013</td>
<td>Abdominal pain</td>
<td>862</td>
<td>SMD = −0.24; 95% CI −0.16 to 0.51 *</td>
<td></td>
</tr>
<tr>
<td>McFarland 2008</td>
<td>Global symptoms</td>
<td>1838</td>
<td>OR = 2.24; 95% CI 1.51 to 2.75</td>
<td>8</td>
</tr>
<tr>
<td>McFarland 2008</td>
<td>Abdominal pain</td>
<td></td>
<td>OR = 1.6; 95% CI 1.2 to 2.2</td>
<td></td>
</tr>
<tr>
<td>McFarland 2008</td>
<td>Abdominal pain</td>
<td></td>
<td>SMD = 0.23; 95% CI 0.07 to 0.38</td>
<td></td>
</tr>
<tr>
<td>McFarland 2008</td>
<td>Abdominal pain</td>
<td></td>
<td>OR = 2.88; 95% CI 1.84 to 4.5</td>
<td></td>
</tr>
<tr>
<td>McFarland 2008</td>
<td>Abdominal pain</td>
<td>1254</td>
<td>RR = 0.77; 95% CI 0.62 to 0.94</td>
<td>7.3</td>
</tr>
<tr>
<td>McFarland 2008</td>
<td>Abdominal pain</td>
<td>1039</td>
<td>RR = 0.78; 95% CI 0.69 to 0.88</td>
<td>8.9</td>
</tr>
<tr>
<td>Horvath 2011</td>
<td>Abdominal pain in children treated with L. rhamnosus</td>
<td>167</td>
<td>RR = 1.7; 95% CI 1.27 to 2.27</td>
<td>4</td>
</tr>
</tbody>
</table>

*A average of responses to specific organisms

L. rhamnosus in children with IBS and reported a significant benefit for pain improvement.

Mayer et al. Gastroenterology. 2014 July
Meta-analyses of Probiotics in IBS

Meta analyses highlight the problems interpreting results from probiotic studies in IBS.

These include:
- inadequate sample size,
- poor study design (e.g., crossover with inadequate washout between study periods),
- inclusion of different IBS subtypes
- the use of multiple strains
- doses across studies.

Mayer et al. *Gastroenterology*. 2014 July
### Probiotic strains: Effectiveness in IBS

**Specific strain**

<table>
<thead>
<tr>
<th>Strain</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bifidobacterium infantis B35624</strong></td>
<td>B *</td>
</tr>
<tr>
<td><strong>VSL#3 (composite containing multiple strains):</strong></td>
<td>B *</td>
</tr>
<tr>
<td>• 3 strains of <em>Bifidobacterium</em>: <em>Bifidobacterium longum</em></td>
<td></td>
</tr>
<tr>
<td><em>Bifidobacterium infantis</em>, <em>Bifidobacterium breve</em></td>
<td></td>
</tr>
<tr>
<td>• 4 strains of <em>Lactobacillus</em>: <em>Lactobacillus acidophilus</em>, <em>Lactobacillus casei</em>, <em>Lactobacillus bulgaricus</em>, <em>Lactobacillus plantarum</em></td>
<td></td>
</tr>
<tr>
<td>• 1 strain of <em>Streptococcus salivarius</em>, subspecies <em>Thermophilus</em></td>
<td></td>
</tr>
<tr>
<td><strong>Bifidobacterium animalis</strong></td>
<td>C</td>
</tr>
<tr>
<td><strong>Lactobacillus plantarum 299V</strong></td>
<td>C</td>
</tr>
</tbody>
</table>

* Recommendations for Probiotic Use from a Yale University Workshop

Wall GC, et.al. World J Gastroenterol. 2014
There is, currently, no clinically useful way of identifying whether the microbiota is disturbed in particular patients with irritable bowel syndrome (IBS).

Probiotics have a reasonable evidence base and should be tried, for a period of at least 1 month, at dose recommended by the manufacturer, before a judgment is made about the response to treatment.
• IBS remains one of the most difficult GI disorders to manage regardless of its benign nature,
• Probiotics has long been an alternative to the conventional medicine for the treatment of many diseases,
• Probiotics might play important roles in maintaining gut homeostasis by the modulation of immunity and increasing epithelial barrier function.
• **Probiotics** is an attractive treatment modality: low costs and favorable safety profiles,

• Results of **clinical studies and systemic meta-analyses**: probiotics have beneficial effects in selected patients
But, we have to clarify:

- In which subset of IBS patients probiotics are best effective?
- Which probiotic species and strains are effective?
- Which is preferred: single or mixed probiotics?
- Which dosage and duration of treatment are optimum?
II Brazilian Conference of Prebiotics, Probiotics and Symbiotics

www.preprosim.com.br
16 - 20th JUNE 2015, Sao Paulo city, Brazil