Targeting the Intestinal Microbiota in the Treatment of Gastrointestinal Disorders

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The Human Intestinal Microbiome
ACG 2014 Annual Meeting
October 22, 2014, Philadelphia, PA

Presentation Outline:
• Background
  - The intestinal microbiota in AAD/CDC, IBS, IBD
  - Interventions targeting the intestinal microbiota:
    Diet, probiotics, antibiotics

• Effects of interventions on:
  - The intestinal microbiota
  - Clinical outcome

• Conclusions and personal perspective
The Intestinal Microbiome in GI Disorders

Intestinal dysbiosis is associated with various intestinal and systemic diseases

- Obesity
- Metabolic syndrome
- Antibiotic-associated Diarrhea (AAD)
- Irritable bowel syndrome
- Inflammatory bowel diseases
- Liver diseases

- Atherosclerosis
- Type 1 diabetes
- Autism
- Allergy
- Asthma
- Celiac disease

Emerging data demonstrate alterations in intestinal microbiota in various disease conditions (compared to healthy controls) although a causal relationship has not been established.

Bäckhed et al., 2005; Sartor, 2010; Honda and Littman, 2011; Ringel, 2009
Targeting the Microbiome in the Treatment of GI Disorders

The intestinal microbiota in GI disorders
- Antibiotic-associated Diarrhea (AAD)
- Irritable bowel syndrome (IBS)
- Inflammatory bowel disease (IBD)

Important questions:
• Does the intestinal microbiota in patients with a specific disorder (e.g., AAD, IBS, IBD) differ from the microbiota in healthy individuals?
• If the intestinal microbiota does differ, is it an important factor in the pathogenesis of these disorder?
• What are the clinical implications? Can we target the intestinal microbiota in the treatment of these disorders?
The Intestinal Microbiota in IBS

High throughput 454 sequencing on fecal samples

Di-IBS patients

Healthy controls

Overall average abundance of bacterial taxa (genus level)

Faecalibacterium genus

Healthy controls

Di-IBS patients

Concentrations of specific bacterial species

Faecalibacterium prausnitzii

By IBS Subtypes

By Bloating Symptoms

The intestinal microbiota differ among patients with IBS and HC based on characteristics of their bowel habits and the presence of symptoms of abdominal bloating.

Carroll, Ringel-Kulka et al., Neurogastroenterol and Motil 2012

Ringel Y et al., DDW 2014 (MS under review)
The Intestinal Microbiota in IBD

High throughput 454 sequencing on fecal samples

**Microbial composition by disease phenotypes**

- The microbial composition of CD differed from HC.
- Fecal samples from CD patients with ileal disease differed from samples from CD patients with colonic disease.
- No differences were found between UC and HC.

➢ The intestinal microbiota differ between patients with IBD and HC and among patients with different IBD phenotypes.

Willing BP et al., Gastroenterol 2010

Targeting the Microbiota in the Treatment of GI Disorders

**The intestinal microbiota in GI disorders**
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Targeting the Microbiota in the Treatment of GI Disorders

The intestinal microbiota in GI disorders
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- Inflammatory bowel disease (IBD)

Important questions:

→ Does the intestinal microbiota in patients with a specific disorder (e.g., AAD, IBS, IBD) differ from the microbiota in healthy individuals?

=> Microbiology investigations demonstrate compositional changes in the intestinal microbiota of patients with these GI disorders.

Is it important/relevant?
The Intestinal Microbiota & Pathophysiology – AAD

Pathophysiology of *C. difficile* Colitis

```
Antibiotic therapy

Altered colonic microflora

*C. difficile* exposure and colonization

Toxin production

Protective immune response

Asymptomatic carriage

Diarhea and colitis

(“Intestinal Dysbiosis”)
```

The Intestinal Microbiota & Pathophysiology – IBS

Suggested Pathophysiological Model

```
Triggers and Predisposing Factors

Environmental factors
  - Psychological stress
  - Anxiety/Depression

Peripheral:
  - Gastroenteritis
  - Diet
  - Medications
  - Lifestyle

Host factors
  - Genetics
  - Disease conditions

Altered intestinal microbiota
  - Composition
  - Function

Altered intestinal immune system
  - Mast cell activation
  - Inflammatory cytokines

Altered intestinal function
  - Sensory-motor function
  - Barrier function

Functional GI symptoms
```

Ringel Y et al. Am J Physiol Gastrointest Liver 2013

Gastroenterol Clin North Am 2002

ACG 2014 Annual Scientific Meeting
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The Intestinal Microbiota & Pathophysiology – IBD

Suggested Pathophysiological Model

The current disease hypothesis is that the chronic inflammation of IBD results from alterations in the intestinal microbiota and damaged epithelial barrier in a susceptible host with genetically dysregulated immune response to the gut microbiota.

Targeting the Microbiota in the Treatment of GI Disorders

The intestinal microbiota in GI disorders
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Important questions:

- Does the intestinal microbiota in patients with a specific disorder (e.g., AAD, IBS, IBD) differ from the microbiota in healthy individuals?
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- What are the clinical implications? Can we target the intestinal microbiota in the treatment of these disorders?

Cerf-Bensussan et al. Nature Review Immunology 2010
Targeting the Microbiota in the Treatment of GI Disorders

The intestinal microbiota in GI disorders
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Important questions:
- Does the intestinal microbiota in patients with a specific disorder (e.g., AAD, IBS, IBD) differ from the microbiota in healthy individuals?
- If the intestinal microbiota does differ, is it an important factor in the pathogenesis of these disorder?

=> There is a growing body of evidence that alterations in the intestinal microbiota ("intestinal dysbiosis") is an important factor in the pathophogenesis of these disorders.

Targeting the Microbiota in the Treatment of GI Disorders

The intestinal microbiota in GI disorders
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- Irritable bowel syndrome (IBS)
- Inflammatory bowel disease (IBD)

Important questions:
- Does the intestinal microbiota in patients with a specific disorder (e.g., AAD, IBS, IBD) differ from the microbiota in healthy individuals?
- If the intestinal microbiota does differ, is it an important factor in the pathogenesis of these disorder?
- Can we target the intestinal microbiota in the treatment of these disorders?
## Targeting the Microbiota in the Treatment of GI Disorders

### Factors that can influence the gut microbiome

<table>
<thead>
<tr>
<th>Factor</th>
<th>Evidence from:</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of delivery</td>
<td>Humans</td>
<td>(Domínguez-Flétel et al., 2010; Palmer et al., 2007)</td>
</tr>
<tr>
<td>Host genotype</td>
<td>Humans</td>
<td>(Spör et al., 2011) and references therein</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>(Kovacs et al., 2011; Ley et al., 2005; Benson et al., 2010)</td>
</tr>
<tr>
<td>Geographic origin</td>
<td>Humans</td>
<td>(De Filippis et al., 2010)</td>
</tr>
<tr>
<td></td>
<td>Macaques</td>
<td>Seeker, Sætren and Fraser (unpublished data)</td>
</tr>
<tr>
<td>Diet</td>
<td>Humans</td>
<td>(Wu et al., 2011; Walker et al., 2011)</td>
</tr>
<tr>
<td></td>
<td>Animals</td>
<td>(Tumaugh et al., 2006; Hildebrandt et al., 2009)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Humans</td>
<td>(Willig et al., 2011a; Jamborg et al., 2007; Deltikieken and Fa rename, 2011)</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>(Yap et al., 2008; Cani et al., 2008)</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Humans</td>
<td>(Rauch and Lynch, 2011) and references therein</td>
</tr>
<tr>
<td></td>
<td>Animals</td>
<td>(García-Mazari et al., 2011)</td>
</tr>
<tr>
<td>Age</td>
<td>Humans</td>
<td>(Thomson et al., 2010) (Bagi et al., 2010)</td>
</tr>
<tr>
<td>Stress</td>
<td>Humans</td>
<td>(Konturek et al., 2011) and references therein</td>
</tr>
</tbody>
</table>

Fecal Microbiome Transplant (FMT)

- *C. difficile*
- Ulcerative colitis
- IBS?
- Other conditions?
Targeting the Microbiota in the Treatment of GI Disorders

Interventions targeting the intestinal microbiota
- Diet
- Probiotics
- Antibiotics

• Effects of these interventions on:
  - The intestinal microbiota
  - Clinical outcome
Intestinal Microbiota – Effects of Diet

- A controlled-feeding study of 10 subjects with high-fat/low-fiber or low-fat/high-fiber diet.
- Intestinal microbiota was investigated by 454 sequencing of the 16S rDNA gene.
- Correlation of diet with changes in the gut microbial taxa over 10 days.

- Columns - bacterial taxa
- Rows - nutrients measured by dietary questionnaire
- Red - positive association / Blue - negative association
- The intensity of the colors - the degree of association between the taxa abundances and specific nutrients

Wu GD et al., Science 2012

Intestinal Microbiota – Effects of Probiotics

- Fecal samples from 18 healthy adults pre- and post-intervention with commercially available probiotics containing either Bifidobacterium or Lactobacillus strains.

Table 1. Phylum-level species assignment of OTUs showing significant fold change or quantity difference by administration of probiotics

<table>
<thead>
<tr>
<th>Type of probiotics</th>
<th>Change</th>
<th>Number of varied OTUs</th>
<th>Fold change (≥10-fold)</th>
<th>Difference (≥150 reads)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Firmicutes</td>
<td>Actinobacteria</td>
<td>Bacteroidetes</td>
</tr>
<tr>
<td>Lactobacillus</td>
<td>Increase</td>
<td>9</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>7</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>16</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Bifidobacterium</td>
<td>Increase</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>9</td>
<td>9</td>
<td>0</td>
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<tr>
<td>All</td>
<td>Increase</td>
<td>14</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>11</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>25</td>
<td>19</td>
<td>1</td>
</tr>
</tbody>
</table>

only OTUs with a P-value < 0.05 are shown

- Species belonging to the Firmicutes were affected by both Lactobacillus and Bifidobacterium

Kim S-W et al., DNA Research 2013
Intestinal Microbiota – Effects of Probiotics

- Fecal samples from 18 healthy adults pre- and post-intervention with commercially available probiotics containing either *Bifidobacterium* or *Lactobacillus* strains.

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<th>Difference (≥250 reads)</th>
</tr>
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<tbody>
<tr>
<td><em>Lactobacillus</em></td>
<td>Increase</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
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<td>7</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>Bifidobacterium</em></td>
<td>Increase</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td>Increase</td>
<td>14</td>
<td>12</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td>3</td>
<td>1</td>
<td>1</td>
</tr>
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<td>6</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>4</td>
<td>4</td>
<td>0</td>
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<td>1</td>
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- Species belonging to the Firmicutes were affected by both *Lactobacillus* and *Bifidobacterium*
- Species belonging to the Bacteroidetes were affected only by *Lactobacillus* probiotics

Kim S-W et al., DNA Research 2013

UNC School of Medicine

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Intestinal Microbiota – Effects of **Probiotics**

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<th>Number of varied OTUs</th>
<th>Difference (≥350 ROC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lactobacillus</em></td>
<td>Increase 9</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Decrease 7</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td><em>Bifidobacterium</em></td>
<td>Increase 5</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Decrease 4</td>
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<tr>
<td>All</td>
<td>Increase 14</td>
<td>12</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Decrease 11</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>0</td>
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- Species belonging to the Firmicutes were affected by both *Lactobacillus* and *Bifidobacterium*
- Species belonging to the Bacteroidetes were affected only by *Lactobacillus* probiotics

- Probiotics affect the composition of the intestinal microbiota and this effect is strain specific.

Kim S-W et al., DNA Research 2013

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Intestinal Microbiota – Effects of **Antibiotics**

Bacterial community shifts and waves of succession following Clindamycin, inoculation with *C. difficile*, and administration Vancomycin.

Peterfreund GL et al PLOS ONE 2012
Bacterial community shifts and waves of succession following clindamycin administration, inoculation with *C. difficile*, and Vancomycin treatment.

Intestinal Microbiota – Effects of Antibiotics

- Exposure to clindamycin leads to profound reduction in abundance of Bacteroidetes and Firmicutes.
### Intestinal Microbiota – Effects of Antibiotics

- Exposure to clindamycin leads to profound reduction in abundance of Bacteroidetes and Firmicutes.

- Further treatment with Vancomycin prolonged the effects of clindamycin by extending the knockdown of certain members of the intestinal microbiota.

- Some additional changes with inoculation with *C. difficile*.

---

<table>
<thead>
<tr>
<th>Days post-induction</th>
<th>Proteobacteria</th>
<th>Firmicutes</th>
<th>Bacteroidetes</th>
<th>Verrucomicrobia</th>
<th>Tenericutes</th>
<th>Actinobacteria</th>
<th>Anaerococcales</th>
<th>Faecalibacterium prausnitzii</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>1</td>
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<tr>
<td>2</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

**Notes:**
- Exposure to clindamycin leads to profound reduction in abundance of Bacteroidetes and Firmicutes.
- Further treatment with Vancomycin prolonged the effects of clindamycin by extending the knockdown of certain members of the intestinal microbiota.
- Some additional changes with inoculation with *C. difficile*.

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**References:**
- Peterfreund GL et al PLOS ONE 2012

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**Image Source:**
- UNC School of Medicine

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Interventions targeting the intestinal microbiota

- Diet
- Probiotics/prebiotics
- Antibiotics

• Effects of these interventions on:
  - The intestinal microbiota
  ➔ - Clinical outcome
Targeting the Intestinal Microbiota – Clinical Effects

FODMAP Diet in IBS
FODMAPs = Fermentable oligo- (fructans and galactans), di-(lactose), monosaccharide (fructose), and polyols; rapidly fermentable short-chain carbohydrates

Low FODMAP vs. standard diet in IBS

- The low FODMAP diet can significantly improve functional GI symptoms


Targeting the Intestinal Microbiota – Clinical Effects

Low FODMAP vs. Australian Diet in IBS

Effect on overall gastrointestinal symptoms

- “Low FODMAP diet is an effective treatment of functional GI symptoms in IBS”.
- “The lack of effect in healthy controls suggest that the benefits of this intervention is specific for the condition.”

Targeting the Intestinal Microbiota – Clinical Effects

Low FODMAP vs. Australian Diet in IBS

Effect on specific gastrointestinal symptoms

- "These results support the notion that the low FODMAP diet has efficacy in the vast majority of patients with IBS and support its use as a first-line therapy"

The low FODMAP diet may have long term nutritional implications and can significantly reduce the levels of beneficial bacteria.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>P</th>
<th>Control</th>
<th>Intervention</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bacteria</td>
<td>9.7 (9.5–9.8)</td>
<td>9.7 (9.6–9.9)</td>
<td>0.52</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bacteroides-Prevotella</td>
<td>8.7 (8.6–8.9)</td>
<td>8.8 (8.6–8.9)</td>
<td>0.52</td>
<td>17.4 (9.2–25.3)</td>
<td>15.2 (6.2–24.3)</td>
<td>0.72</td>
</tr>
<tr>
<td>E. rectale-C. coccoides</td>
<td>8.8 (8.6–8.9)</td>
<td>8.7 (8.6–8.9)</td>
<td>0.89</td>
<td>15.7 (10.9–20.5)</td>
<td>11.8 (6.6–17.0)</td>
<td>0.27</td>
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<tr>
<td>F. prausnitzii</td>
<td>8.8 (8.6–8.9)</td>
<td>8.8 (8.5–9.0)</td>
<td>0.58</td>
<td>17.9 (13.3–22.6)</td>
<td>13.1 (8.0–18.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Bifidobacteria</td>
<td>8.2 (7.9–8.5)</td>
<td>7.4 (7.1–7.7)</td>
<td>&lt;0.001</td>
<td>3.2 (1.8–5.8)</td>
<td>0.5 (0.2–0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactobacillus, enterococcus</td>
<td>7.4 (7.1–7.7)</td>
<td>7.4 (7.1–7.7)</td>
<td>0.98</td>
<td>1.0 (0.7–1.4)</td>
<td>0.6 (0.2–1.1)</td>
<td>0.17</td>
</tr>
</tbody>
</table>
### Targeting the Intestinal Microbiota – Clinical Effects

#### Diet in IBD

**Enteral nutritional therapy for induction of remission in Crohn’s disease**

Mary Zachos, Melody Tondeur, Anne Marie Griffiths

**The outcome:** induction of remission of active Crohn’s disease

**Data analyzed:** 15 studies, 334 patients.

**Main results:**
- Analyses performed to evaluate the different types of diet (elemental, non-elemental, fat content etc.) demonstrated **no significant difference in efficacy**.
- Meta-analysis of 6 trials compared enteral nutrition (n=192) with steroids (n=160) favored steroids therapy (pooled OR of 0.33; 95% CI 0.21 to 0.53).

**Authors’ conclusions**

“Corticosteroid therapy is more effective than enteral nutrition for inducing remission of active Crohn’s disease (as was found in previous systematic reviews).”

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### Targeting the Microbiota in the Treatment of GI Disorders

**Interventions targeting the intestinal microbiota**

- Diet
  - Probiotics
  - Antibiotics

**Effects of these interventions on:**

- The intestinal microbiota
- Clinical outcome
Targeting the Intestinal Microbiota – Clinical Effects

The outcome: Incidence of diarrhea secondary to antibiotic use

Data analyzed: 16 studies, 3432 patients.

Main results:
- Results from 15/16 studies showed a large, precise benefit from probiotics compared to active, placebo or no treatment control.
- The incidence of AAD in the probiotic group was 9% compared to 18% in the control group (RR 0.52 (95%CI 0.38 to 0.72)).
- None of the 11 trials (n = 1583) that reported on adverse even (AE) documented serious AE.

Authors’ conclusions
- “The overall evidence suggests a protective effect of probiotics in preventing AAD”
- “The benefit for high dose probiotics (L. rhamnosus or S. boulardii) needs to be confirmed”
- “It is premature to draw conclusions about the efficacy and safety of other probiotic agents.”
Yehuda Ringel, MD, FACG

**Targeting the Intestinal Microbiome – Clinical Effects**

**Probiotics in IBS**

<table>
<thead>
<tr>
<th>Study population</th>
<th>Treatment</th>
<th>Control</th>
<th>RR odds ratio 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Probiotics</td>
<td>Placebo</td>
<td>0.72 (0.57-0.88)</td>
<td>39.96</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Probiotics</td>
<td>Placebo</td>
<td>0.71 (0.54-0.92)</td>
<td>19.25</td>
</tr>
<tr>
<td>Global Symptoms</td>
<td>Probiotics</td>
<td>Placebo</td>
<td>0.72 (0.57-0.88)</td>
<td>39.96</td>
</tr>
</tbody>
</table>

- Overall RR of not improving Global Symptoms Scores (GSS) 0.72 (95% CI 0.57-0.88)

Moayyedi P et al., Gut 2010
Targeting the Intestinal Microbiome – Clinical Effects

Probiotics in IBS

Relative risk of persistent IBS Symptoms probiotics vs. placebo

<table>
<thead>
<tr>
<th>Study category</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus</td>
<td>n=3; 140 pts</td>
<td>0.72 (0.57-0.88)</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>n=4; 302 pts</td>
<td>0.57 (0.41-0.79)</td>
<td></td>
</tr>
<tr>
<td>Bifidobacterium</td>
<td>n=2; 422 pts</td>
<td>0.69 (0.53-0.89)</td>
<td></td>
</tr>
<tr>
<td>Streptococcus</td>
<td>n=1; 54 pts</td>
<td>0.67 (0.57-0.81)</td>
<td></td>
</tr>
</tbody>
</table>

Moayyedi P et al., Gut 2010

Overall RR of not improving Global Symptoms Scores (GSS) 0.72 (95% CI 0.57-0.88)

Targeting the Intestinal Microbiome – Clinical Effects

Probiotics in IBS

“The currently available data, from well-designed randomized controlled clinical trials, is still limited and is not sufficient to support a general recommendation for the use of probiotics or a specific probiotic bacteria/product in patients with IBS.”

“In view of the paucity of available treatments for IBS, the overall safety of probiotics lowers the bar for trying probiotics in patients with IBS and possibly other functional GI disorders.”

“When choosing a product for such patients, it is recommended that providers and patients look for products that were specifically tested in IBS.”

Ringel Y et al, Am J Gastroenterol 2012
Ringel Y, Ringel-Kulka T J Clin Gastroenteral 2011
Targeting the Intestinal Microbiome – Clinical Effects

Probiotics in IBD

Pouchitis

- Delay of the first onset of pouchitis by *Lactobacillus rhamnosus* GG
  
  *Gosselink MP, Dis Colon Rectum 2004*

- Maintenance of remission of recurrent or refractory pouchitis by VSL#3
  
  *T Mimura, Gut 2004*

Ulcerative Colitis

- May be beneficial for maintenance as adjuvant therapy (not as a first line)
- More studies are needed

Crohn's Disease

- Currently there is no support for the use of probiotics in Crohn’s disease
  
  *Guandalini A et al, Expert Rev Clin immunol 2010*
  
  *Ringel Y et al, Am J Gastroenterol 2012*

Targeting the Microbiota in the Treatment of GI Disorders

Interventions targeting the intestinal microbiota

- Diet
  - Probiotics/prebiotics
  
  ➜ - Antibiotics

- Effects of these interventions on:
  - The intestinal microbiota
  
  ➜ - Clinical outcome
Targeting the Intestinal Microbiome – Clinical Effects

Antibiotics in IBS

- Phase 3, double-blind, placebo-controlled trials on 1,260 patients with mild-to-moderate, non-constipating IBS symptoms treated with rifaximin 550mg vs. placebo for 2 weeks and followed 3-months.

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>Proportion of Patients with a Response</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value for Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo, n=414</td>
<td>Rifaximin, n=419</td>
<td></td>
</tr>
<tr>
<td>Weeks global IBS symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TARGET 1</td>
<td>98/314</td>
<td>101/319</td>
<td>3.53 0.01</td>
</tr>
<tr>
<td>TARGET 2</td>
<td>101/319</td>
<td>116/315</td>
<td>3.45 0.03</td>
</tr>
<tr>
<td>Combined</td>
<td>201/634</td>
<td>217/634</td>
<td>1.49 &lt;0.001</td>
</tr>
<tr>
<td>Weekly IBS-related bloating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TARGET 1</td>
<td>90/314</td>
<td>122/319</td>
<td>1.62 0.005</td>
</tr>
<tr>
<td>TARGET 2</td>
<td>102/319</td>
<td>119/315</td>
<td>1.49 0.02</td>
</tr>
<tr>
<td>Combined</td>
<td>192/634</td>
<td>241/634</td>
<td>1.56 &lt;0.001</td>
</tr>
</tbody>
</table>

- Adequate relief of IBS symptoms achieved more frequently in the active compared to placebo arm (40.7% vs. 31.7%, P=0.0008); NNT = 11


Antibiotics can provide short-term clinical benefits in some patients with IBS

- The mechanisms by which antibiotics induce beneficial effect/s are not clear and may extend beyond direct effects on the composition of the gut microbiota

DuPont HL, AP&T 2014
Targeting the Intestinal Microbiome – Clinical Effects

Antibiotics in IBD

In Crohn's Disease:
- For active CD (10 RCTs, 1,160 pts) - antibiotics is superior to placebo (RR of active CD not in remission = 0.85; 95 % CI, P = 0.03).
- In perianal CD fistula (3 RCT, 123 pts) - a statistically significant effect in reducing fistula drainage (RR = 0.8; 95 %, P=0.05).
- For quiescent CD (3 RCTs, 186 pts) - a statistically significant effect in favor of antibiotics vs. placebo (RR of relapse = 0.62; 95 % CI, P=0.03).

In Ulcerative Colitis:
- In active UC (9 RCTs, 662 pts) - a statistically significant benefit for antibiotics inducing remission (RR of UC not in remission = 0.64; 95 % CI, P=0.05).

- Antibiotics may induce remission in active CD and UC, although data are difficult to interpret due to the diverse number of antibiotics tested.
- “This systematic review is a mandate for further trials of antibiotic therapy in IBD.”

Khan KJ et al., Am J Gastroenterol 2011
Targeting the Microbiota in the Treatment of GI Disorders

Presentation Outline:

- **Background**
  - The intestinal microbiota in AAD, IBS, IBD
  - Interventions targeting the intestinal microbiota:
    - Diet, probiotics, antibiotics

- **Effects of interventions on:**
  - The intestinal microbiome
  - Clinical outcome

- **Conclusions and personal perspective**

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Summary of Current Knowledge

- Interventions targeting the intestinal microbiota e.g., diet, probiotics and antibiotics, have a potential to:
  - Alter the composition and function of the intestinal microbiota
  - Affect intestinal functions that are relevant to the pathogenesis of certain GI disorders (motility, sensation, innate immunity, metabolic activity)
  - Induce beneficial clinical effect/s

✔ There is a rationale for targeting the intestinal microbiota in the treatment of GI disorders.
Limitations and gaps in knowledge

• There is a discrepancy in the quality of the data coming from *in-vitro* and animal studies and the data from clinical human studies.

• Most of the clinical trials on interventions targeting the intestinal microbiota focused on clinical endpoints and did not include microbiome investigations.

• Most of the human microbiome research has focused on compositional (phylotyping) research and less on microbial functionality, mechanisms of effect and clinical relevance.

Unresolved questions:

• Are the observed altered microbial composition a cause or a bystander?

• What are the mechanisms by which the altered intestinal microbiota lead to abnormal GI function and symptoms?

• Who are the preferred targeted patients?

• What are the preferred, most effective and safe interventions and regimens?

• What is the expected magnitude of benefit?

Need more high quality clinical, microbial and mechanistic research!
Thank you