The Microbiome and Functional Gastrointestinal Disorders

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Irritable Bowel Syndrome (IBS)
A Changed Perspective

- Common world wide and a health care burden
- Can be disabling
- Varying phenotype
- Etiology unclear but gut-brain axis thought to play a pivotal role and new avenues being explored
- Therapeutic options remain limited, but considerable progress and interest
IBS Pathophysiology

- Heredity; nature vs nurture
- Dyssmotility, “spasm”
- Visceral Hypersensitivity
- Altered CNS perception of visceral events
- Psychopathology
- Infection/Inflammation
- Altered Microbiota
- Diet
Evidence for a role for the Microbiota in IBS

- **Direct evidence of an altered gut flora:**
  - Post-Infectious IBS (PI-IBS)
  - Small Intestinal Bacterial Overgrowth (SIBO)
  - Altered Colonic Flora

- **Evidence of physiological effects of an altered flora:**
  - Changes in stool volume/consistency
    - Bile salt deconjugation
  - Alterations in gas volume/composition
    - Fermentation
    - Food-microbiota interactions

- **Mediator of pro-inflammatory state**

- **Therapeutic impact of altering flora**

Post-Infectious IBS

- **10-35% incidence following confirmed bacterial gastroenteritis**

- **Risk factors**
  - Female
  - Severe illness
  - Pre-morbid psyche
    - Depression
  - Persistent inflammation
    - EC cells
    - T lymphocytes
  - Genetic predisposition

Lessons from PI-IBS

- Disturbed Flora
- Inflammatory Response
- Susceptible Host

SYMPTOMS

Myo-Neural Dysfunction

IBS

High-throughput Sequencing of the Microbiota

Large overlap in the two populations

Jeffery et al, Gut 2012;61:997-1006
Correlation-based clustering of subjects by microbiota composition

Two IBS specific clusters

Revised Groupings

The two IBS specific clusters are similar

Jeffery et al, Gut 2012;61:997-1006
Clinical Associations

Early-Life Dysbiosis - Adult Visceral Hypersensitivity
Percentage of reads classified at phylum level

Vehicle 10mg/kg 30mg/kg 100mg/kg Vehicle 10mg/kg 30mg/kg 100mg/kg

Bacteroidetes Firmicutes Proteobacteria Tenericutes
Actinobacteria Epsilonbacteria Lentisphaeraceae Unclassified

Response to Colo-Rectal Distension at 9-12 weeks

Pressure of distension (mmHg)

Vehicle 10mg/kg 30mg/kg 100mg/kg

Disruption of the Microbiota in early life leads to a permanent change in enteric neurophysiology

O’Mahony et al DDW 2009
Can we link the microbiota and inflammation in IBS?

- Anti-Flagellin antibodies (but not ANCA or ASCA)
- Increased levels of β-defensin
- Toll-like receptor (TLR) activation

Shanahan F. Science & Medicine 2003
Up-Regulation of TLR’s in IBS

Brint et al. Am J Gastroenterol 2011;106:329-36

- TLR3
- TLR4
- TLR7
- TLR8

Diet and IBS

Perceived food intolerance
90% IBS vs 55% control

Dietary restrictions
92% IBS vs 46% control

- Cereals: 53%
- Spicy foods: 39%
- Vegetables: 36%
- Fatty foods: 36%

- Milkproducts: 9.6%
- Vegetables: 7.4%
- Fruit: 5.2%

- Only a small proportion sought professional healthcare advice on dietary restrictions

Hayes et al, J Clin Nut Diet 2013 [epub ahead of press]
Why does food provoke symptoms in IBS?

• **Dietary components**
  – Tryptophan
    • Depletion/augmentation can influence anxiety and GI symptoms in IBS

• **Food allergy**

• **Food intolerance**
  – Gluten
  – **FODMAPs**

• **Interaction with the gut microbiome**

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Rifaximin in IBS

• 1,260 patients with non-constipation IBS recruited in US and Canada

• **Rifaximin 550 mg, 3 times daily** for 2 weeks

• Primary endpoint:
  – Proportion who achieved adequate relief of IBS symptoms for ≥2 weeks during the first 4 weeks of the 10-week follow-up phase

• Also assessed relief of IBS bloating and symptom responses at 12 weeks

Endpoints Target 1 Target 2 Combined
Adequate relief of IBS symptoms
Rif vs Placebo 41% vs 31% 41% vs 32% 41% vs 32%
Adequate relief of IBS bloating
Rif vs Placebo 40% vs 29% 41% vs 32% 40% vs 30%
All p<0.03

Why does Rifaximin work in IBS?

1. SIBO
   – May not be common
   – Not assessed in large trials
   – Benefit not dependent on abnormal LHBT
2. Effects on colonic flora
3. Anti-inflammatory effect

Quigley EM. Gastroenterology 2011;141:391-3.
Probiotics

- First described by Metchnikoff in 1908
- “Live microbial food ingredients that alter the microflora and confer health benefit” (FAO)

Is a “live” organism necessary?
- Dead cells
- Bacterial Components
- Bacterial products
  - Peptides
  - Metabolites
- Bacterial DNA

May all have biological effects!

Should we use the term pharmabiotic rather than probiotic?
**Probiotics in IBS**

- McFarland LV and Dublin S. (World J Gastroenterol 2008;14:2650-61)
  - 20 RCT’s, 1982-2007, n=1414
  - Global IBS Symptoms: RR 0.77 (0.6-0.94)
  - Abdo Pain : RR 0.78 (0.69-0.88)

- Nikfar S, et al. (Dis Colon Rectum 2008;51:1775-80)
  - 8 RCT’s, 1966-2007
  - Clinical improvement: RR 1.22 (1.07-1.4)

- Moayyedi P, et al. (Gut 2010;59:325-32)
  - 20 RCT’s, 1966-2008, n=1628
  - Outcomes as a dichotomous variable 11 RCTs (n=936)
    - RR of IBS not improving = 0.71; 95% CI = 0.57 to 0.87, NNT = 4
  - IBS score as a continuous outcome 15 RCT’s (n=1351)
    - SMD = -0.34; 95% CI -0.60 to -0.07

**Bifidobacterium infantis 35624 in IBS**

- 362 females with IBS recruited in primary care
  - Bristol stool score >2, < 7
  - 4 weeks treatment with:
    - *Bifidobacterium*, $10^6$, $10^8$, $10^{10}$
    - Placebo
  - Symptoms recorded by IVRS

Global Assessment of Symptom Relief

% Answering “Yes” at Week 4

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Answering “Yes”</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. infantis 1X10⁰</td>
<td>30</td>
</tr>
<tr>
<td>B. infantis 1X10⁶</td>
<td>60</td>
</tr>
<tr>
<td>B. infantis 1X10⁸</td>
<td>40</td>
</tr>
<tr>
<td>Placebo</td>
<td>30</td>
</tr>
</tbody>
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P=0.0118

Bifidobacterium lactis DN-173 010

Probiotic-Related Changes in Brain Responses

Tillisch et al. Gastroenterology 2013;144:1394-1401

Longer term use

L GG, L rhamnosus, Bif Breve Propionibacterium freudenreichii

Abdo Pain
Distension
Flatulence
Borborygmi

Prebiotics

• “Non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of one species or a limited number of species of bacteria in the colon”
  – Oligosaccharides in human breast milk
  – Inulin
  – Fructose oligosaccharides
    • Promote growth of bifidobacteria and lactobacilli

Microbiota Transplantation

• *C difficile*
• Metabolic syndrome
• Constipation and IBS
• .........................
Summary

• IBS, a variable amalgam of common gastrointestinal symptoms, is an important global issue

• Though incompletely understood, it is clear that luminal (food and the microbiota), environmental (stress) and intrinsic (psychological status, gender) conspire to induce and precipitate symptoms

• Evidence for immune activation in the systemic compartment continues to accumulate: changes at the mucosal level may be more complex

• Alterations in the microbiota or in microbiota-host interactions could explain some symptoms in IBS or lead to immune activation which could, in turn, influence local and central pathways

• These findings may open new therapeutic avenues in IBS