Is There A Role For Gut Flora In IBS?

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Intestinal Microbiota

• Colonized from birth
• Microbiota is subject-specific and stable
• Two distinct ecosystems
  – Luminal bacteria associated with feces or food
  – Mucosa associated bacteria
Working Hypothesis

• Abnormal microbiota activate mucosal innate immune responses
  – Increase epithelial permeability
  – Activate nociceptive sensory sensory pathways
  – Dysregulate enteric nervous system
• Metabolic capacity
• Qualitative or quantitative differences
  – Post infectious IBS
  – SIBO are implicated in subgroups of FBD patients
Oral cavity
200 species

Stomach
*Helicobacter pylori*

Duodenum and proximal jejunum
$10^2 - 10^3$ bacteria/mL

Ileum
$10^8$ bacteria/mL

Colon
$10^{10} - 10^{11}$ bacteria/g
400-500 species including
- *Bacteroides*
- *Eubacterium*
- *Peptostreptococcus*
- *Bifidobacterium*
- *Ruminococcus*
- *Bacillus*
- *Fusobacterium*
- *Clostridium*
- *Lactobacillus*
- *Enterococcus*
- *Enterobacter*
# Intestinal Microbiota

<table>
<thead>
<tr>
<th>Intrinsic Factors</th>
<th>Extrinsic Factors</th>
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</thead>
<tbody>
<tr>
<td>Gastric acid</td>
<td>Diet, Pre and Probiotics</td>
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<tr>
<td>$O_2$</td>
<td>PPIs, H2 blockers</td>
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<tr>
<td>Motility</td>
<td>Antibiotics</td>
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<tr>
<td>Mucus</td>
<td>Prokinetics</td>
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<td>GI secretions</td>
<td>Laxatives</td>
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<tr>
<td>Antimicrobial peptides</td>
<td>Opioids</td>
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<td>Immunity (sIgA)</td>
<td>NSAIDs</td>
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Approaches to the Study of Intestinal Microbiota

• Lack of selective growth media
• Breath tests are not validated
• Rapid molecular approaches have largely replaced cultural approaches
• Cultural microbiology remains crucial for investigating microbial diversity and select isolation of pathogens
Approaches to the Study of Intestinal Microbiota

- Rapid molecular approaches have largely replaced cultural approaches
  - Diversity of microbes
    - 16S rRNA
    - FISH
  - Microbial genes: Metagenomics
    - Sequencing of genes from whole microbial environments at once
Metabolic Activities of Intestinal Microbiota

- Biotransformation of bile acids
- Breakdown of dietary oxalate
- Conversion of prodrugs to active metabolites
- Degradation of polysaccharides of plant origin
- Production of folate, B vitamins, and vitamin K
- Production of SCFA
- Production of regularotry signals for mucosal and immune homeostasis
- Regulation of fat storage
Immune Microbial Interactions

• Toll-like receptors (TLRs) are present on epithelial and dendritic cells
• In health, engagement of TLRs with commensal microbiota is required for mucosal homeostasis
Post Infectious IBS

- Infective gastroenteritis produces a profound depletion of commensal microbiota -> SCFAs
- 6% - 17% IBS report onset of symptoms after gastroenteritis
- Meta analysis increase risk of IBS 1 year after bacterial gastroenteritis
  - RR=6.5 CI (2.6-15.4)

Longstreth GF. *Aliment Pharmacol Ther* 2001;15:959-64
Thabane M. *Aliment Pharmacol Ther* 2007;26:535-44
Post Infectious IBS

• Increase of mucosal cytotoxic T lymphocytes
• Increase in enteroendocrine cells
• Study of children gastroenteritis
  – Alkalisation of stool pH
  – Fall in numbers of *Bacteroides, Bifidobacterium, Lactobacillus and Eubacterium*

Small Intestinal Bacterial Overgrowth

• Role of SIBO in pathogenesis of IBS is controversial
• Breath tests have not been validated
• “Gold standard” of jejunal cultures $> 10^5$ cfu/ml has been challenged
Test meal
10 g Lactulose
+ 20 MBq $^{99mTc}$-sulfur colloid

Colonic fermentation: $H_2$ gas

$99mTc$ radioactivity

Expired $H_2$ gas ppm

Gamma camera collimator

Threshold for abnormal $H_2$ breath test

Cecal radioactivity
Breath hydrogen (ppm)

Minutes

0  90  180
Modulation of Intestinal Microbiota

• A short course of non-absorbable antibiotic such as Rifaximin in IBS-D
  – Improves bloating and flatulence
• Majority of trials of probiotics in IBS show some degree of efficacy
• Prebiotics and synbiotics should theoretically have the potential in treating FGD
Overall improvement of global IBS symptoms with Rifaximin during 10 weeks of follow up
Mechanism of Action

- Reduction of overall bacterial load
  - SIBO vs alteration of colonic flora/fermentation
- Decreased bacterial fermentation
- Less bloating
- Not FDA approved for the treatment of IBS
Probiotics

- Live microorganisms
- Lactobacilli and bifidobacteria
- Visceral hypersensitivity, GI dysmotility, intestinal permeability, intestinal microbiota and immune function
- *Bifidobacterium infantis*, *Bifidobacterium lactis* and *Bifidobacterium bifidum*
Prebiotics and Synbiotics

- Prebiotic stimulates the growth of beneficial bacteria already present in the host
- Synbiotic is a combination of prebiotic and probiotic
- Trans-galactooligosaccharide mixture
  - Reduced symptoms and stimulated growth of bifidobacteria
<table>
<thead>
<tr>
<th>Fructans and Galactans</th>
<th>Polyols</th>
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<tbody>
<tr>
<td>Fructose</td>
<td>Sorbitol</td>
</tr>
<tr>
<td>Lactose</td>
<td>Xylitol</td>
</tr>
<tr>
<td>Fructooligosaccharide</td>
<td>Mannitol</td>
</tr>
<tr>
<td>Galactooligosaccharide</td>
<td>Maltitol</td>
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FODMAP Guidelines

- Eliminate fructose, honey and sorbitol
- Avoid sugar alcohols found in diet products
- Limit drinks with HFCS
- Check medications for fructose and sorbitol
Clinical Implications

- There is no clinically useful way of identifying whether the microbiota are disturbed in IBS patients
- Dietary evaluation and exclusion of unabsorbable carbohydrates (FODMAP) and excessive fiber
- Probiotics have reasonable evidence
- Utility of testing for SIBO remains an area of uncertainty
Clinical Implications

• Consideration should be given to discontinuing PPI in those with SIBO
• There is emerging evidence that non-absorbable antibiotics may have the potential to reduce symptoms in some patients with IBS
Conclusions

• Although there is good evidence supporting microbiota is perturbed in patients with IBS, data is lacking on the mechanism
• Most probiotic and antibiotic trials are underpowered and suffer suboptimal design