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USING AND MANIPULATING THE GUT MICROBIOME FOR BETTER CLINICAL OUTCOMES: a Gastroenterologist’s perspective

ILSI SEA Region - Conference: Gut feelings - what can we learn from recent research on gut microbiota?
Australia December 2013
(www.ilsi.org/SEA_Region)
Gut microbiome = organisms & all their related genes

- It is an organ of the body
  - ~2 kg in weight
  - Bacteria alone ~100 trillion
  - 10-fold more cells than humans
  - 150-fold more genes

- Daunting array of nomenclature, methodologies, bioinformatics → out of the comfort zone for Gastroenterologists
How to study gut microbiome

- Culture

- Culture-independent approaches
  - Which microbes (*16S rRNA genes*)
  - What microbial genes (*metagenomics*)
  - What they are doing (other ‘*meta-omics*’ – *transcripts, proteins, small molecules*)

- Function as an organ (*e.g.*, *fermentation*)

- Consider above in light of
  - Geographical & ethnic issues
  - Microenvironmental issues
    - mouth-to-anus variations
    - lumen vs mucosa-associated
How to use microbiota in clinical medicine

- Document dysbiosis (alteration in microbiota composition in association with disease) & act upon it

- Use functional properties of microbiota to
  - Influence disease pathogenesis
  - Influence symptom induction
  - Target therapy

- Manipulate structure of microbiota as a therapy
  - Biotic therapy
    - Antibiotics, Probiotics, Prebiotics, Synbiotics
  - Transplantation
    - Faecal microbiota transfer (FMT)
Document dysbiosis & act upon it

Illness

Faecal microbiology, metabolomics, …

Define dysbiosis & functional deficiencies

Diagnostic help

Define therapy

Prognostic information
Are we there yet?

- There are laboratories performing detailed faecal analysis at great cost to patient
  - Culture-based
  - Culture-independent with some metabolic information

*Interpretation and recommendations are purely speculative ('pseudoscience')*
Are we there yet?

- There are laboratories performing detailed faecal analysis at great cost to patients.

We have a limited understanding of:
- What is normal
- What specific alterations mean – good vs bad vs irrelevant
- How to ‘correct’ alterations

*Interpretation and recommendations are purely speculative (‘pseudoscience’)*
Utilise function of microbiota to influence disease pathogenesis

*Ulcerative colitis*

- Butyrate $\rightarrow$ anti-inflammatory but short $t_{1/2}$
- CHO substrates that favour butyrate production
- Bacteria in lumen & mucous layer (e.g., *F. prausnitzii, C. leptum, C. coccoides, Roseburia*) $\rightarrow$ strong butyrate producers

*Microbiota as a ‘drug’ delivery system*
Fermentation of resistant starch (RS) → butyrate ++++


No ↑ butyrate delivery

RS only
Combine RS with wheat bran (WB)

More starch survives to reach the distal colon (location of most pathology)

RS+WB

Resistant starch (RS)
Wheat bran (WB)

↑butyrate delivery

Effect of dietary carbohydrates on tumour size index in DMH-treated rats

Young et al Gastroenterology 1996
Ulcerative colitis in remission

- Heterogeneous colonic physiology
- Response to fibre supplementation
  - Heterogenous
  - Does not correct deficient fermentation
- Could not explain deficient fermentation by abnormalities of structure of microbiota
- Cannot extrapolate information in healthy controls to patients with ulcerative colitis
Utilise function of microbiota to reduce symptoms

- Short-chain carbohydrates
  - Preferentially fermented by small intestinal bacteria
  - Rapidly fermented by colonic bacteria
  - Gas (H₂, CO₂, CH₄) will be produced

- Distension of lumen is a major trigger for symptoms in IBS due to visceral hypersensitivity

♀poorly absorbed S-C CHOṣ (fodmaps) ➔ ✅symptoms in IBS
Mode of action of FODMAPs

↑ gas production in small & large intestine

Luminal distension

↓ Pain, bloating, distension, constipation &/or diarrhoea

if visceral hypersensitivity
Overall symptoms – IBS (n=30)

Halmos et al, Gastroenterology 2014
But what is reducing FODMAP intake doing to structure of microbiota?

- Habitual diet vs low FODMAP diet
  - Specific ↓*Bifidobacteria* spp (FISH)
    - Staudacher et al J Hum Nutr Diet 2012

- Low vs typical FODMAP intake (all food provided)
  - ↑ diversity in *Clostridium* cluster XIVa (DGGE)
  - ↓ total bacterial abundance
  - ↓ relative abundance of *Akthermansia mucinophila* & *Clostridium coccoides* (>> 5-fold; P<0.001)
  - ↑ relative abundance of *Ruminococcus torques* (~2fold)
    - Halmos et al NSA Conference 2013

Not so good in the long term???
Manipulate structure (& function) of microbiota as therapy

- Biotic therapy
  - Antibiotics
  - Probiotics
  - Prebiotics
  - Synbiotics

- Transplantation
  - faecal microbiota transfer (FMT)
Rifaximin vs placebo in IBS without constipation over 4 weeks

- Bloating
- Global symptoms
- Pain
- Stool consistency

Proportion with response (%)

- Placebo
- Rifaximin

n = 1258

p < 0.001

Pimentel et al NEJM 2011
10 weeks follow-up after rifaximin vs placebo in IBS without constipation over 4 weeks

Pimentel et al NEJM 2011
Probiotics in IBS: Recommendations

- **WGO 2009**
  - Effects are highly strain-specific
  - Lactobacilli not effective
  - Bifidobacteria alone or in some combinations demonstrate some efficacy

- **ACG 2009**
  - In single organism studies, lactobacilli not effective
  - Bifidobacteria alone or in some combinations demonstrate some efficacy
  - Interpretation of literature hampered by difficulties comparing ‘apples with oranges’
A randomized, double-blind, controlled study and pooled analysis of two identical trials of fermented milk containing probiotic *Bifidobacterium lactis* CNCM I-2494 in healthy women reporting minor digestive symptoms

P. Marteau, * D. Guyonnet, † P. Lafaye de Micheaux‡ & S. Gelu§

1º end-point: weekly overall assessment of GI well being
Use functional assessment of microbiota to identify patients suitable for probiotics in IBS?

Lactulose breath hydrogen test to identify those with small intestinal bacterial overgrowth (SIBO)
Lactulose breath test

Minutes

Hydrogen (ppm)
Early rise in breath hydrogen

Marker of SIBO
Randomised double-blind trial of placebo vs *Lactobacillus casei* spp Shirota in IBS + ERBHAL

- 23 probiotic vs 22 placebo

- No differences in
  - Effect on time of first rise of breath hydrogen after lactulose or other breath hydrogen test criteria
  - Overall or specific symptoms
    - All patients
    - Those having correction of ERBHAL

- Conclusion:
  - Presence of ERBHAL cannot be used as a predictor of symptomatic response to Yakult in patients with IBS

*Yao et al NSA Conference 2013*
Is high prebiotic intake health-promoting? *Supplements*

- Normal rats & mice, FOS was ‘prebiotic’ but …..
  - Increased colonic permeability
  - Increased salmonella translocation
  - Worsened severity of salmonella infection
    
    *Bovee-Oudenhoven et al Gut 2003; Petersen et al BMC Microbiol 2009*
  - Reduced *A. mucinphila* in mucus in proximal colon
    
    *Van den Abbeele et al Environ Microbiol 2011*

- Healthy men, FOS
  - No effect on permeability (EDTA)
  - Increased mucus production
    
    *Ten Bruggencate et al J Nutr 2006*
  - ? Good – less degradation, more protection
  - ? Bad – reflection of injury/irritation of epithelium
Prebiotic RCTs in IBS

- **FOS 5 g/d in 105 patients**
  - Intensity of symptoms: \(\text{FOS} 44\% \quad \text{vs} \quad \text{placebo} 14\%\)
  - *Paineau et al. BJN 2008*

- **FOS 10→20 g FOS/d in 98 patients**
  - No benefit ..... Not worse
  - *Olesen et al. AJCN 2000*

- **Synthetic trans-GOS 7 g/day**
  - ↓symptoms + ↑Bifidobacteria
  - *Silk et al. APT 2009*

*No account taken of habitual FOS/GOS intake*
Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn’s disease

Jane L Benjamin,¹ Charlotte R H Hedin,¹ Andreas Koutsoumpas,¹ Siew C Ng,²,³

No attention paid to food-related prebiotic intake

No effect on disease activity

↑ abdominal symptoms

No effect on microbiota
Is high prebiotic intake health-promoting? *Food*

- No studies

- Many foods are naturally rich in oligosaccharides with prebiotic properties
  - Fructans, galacto-oligosaccharides (GOS)
Faecal microbiota transfer

- Fervour of enthusiasm
  - ~90% success in eliminating *C. difficile* in patients failing antibiotic approaches
    - *Mattila et al, Gastroenterology 2012*
    - *Kelly et al, J Clin Gastroenterol 2012*

- Anecdotes of efficacy in many conditions
Effect of FMT on faecal microbiota

Khoruts et al, JCG 2010
Concern re FMT

- Long term consequences are not known
- Composition of gut microbiota appears to be associated with
  - metabolic syndrome
  - cardiovascular disease
  - alteration of drug metabolism
  - brain function
  - ..........

➡️ Only for
  ➡️ resistant *C. difficile* infection
  ➡️ In context of clinical trials (monitor health outcomes)
Questions re gut microbiome

- Is there a healthy gut microbiome?
- Are there causal relationships between gut microbiome and human disease?
- Is there a role for non-bacterial gut microbes in disease?
- What is the optimal way of altering gut microbiota?
- What are the long term effects of manipulation of the microbiota?

How can we use diet/food choice to promote healthy microbiota?

_Wu & Lewis, CGH 2013_
Using and manipulating the gut microbiome for better clinical outcomes

- Exciting, confusing, worrying & in its infancy
- Already being misused (for commercial gain)
- Gastroenterologists and nutrition experts have to up-skill in understanding gut microbiome & take the lead in ensuring its manipulation is scientifically sound, evidence-based & safe